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ANNALS OF INTERNAL MEDICINE

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The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

Editor

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Thrombo-Angiitis Obliterans: A Clinical Study of 200 Cases*

I. Etiology, Pathology, Symptoms, Diagnosis

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SPONTANEOUS gangrene of the feet in middle-aged patients without arteriosclerosis has been known for many years. In 1879 Winiwarter reported the case of a man, aged fifty-seven, who had complained of rheumatic pains in the feet for twelve years. The pathologic changes were intimal proliferation, thrombosis and periarterial fibrosis; arteriosclerosis was absent. He designated the condition as a peculiar type of endarteritis and endophlebitis. Weiss, in 1895, and Manteuffel, in 1897, reported similar cases from which they concluded that the thrombosis was due to intimal changes of an arteriosclerotic nature. In 1879 Borchard reported five cases and favored the view of Winiwarter. Bunge, in 1901, supported the theory of Weiss and Manteuffel, but his cases seem to have been true examples of arteriosclerotic disease in older patients. In 1908 Buerger reported the results of his study of dissected vessels of eleven limbs amputated from middle-aged Hebrews with spontaneous gangrene in which he concluded that the disease was primarily an acute inflammation of the arteries resulting in a cellular type of thrombosis. In the older lesions, organization, canalization, and periarterial fibrosis were observed. Because of the inflammatory thrombotic nature of the disease he called it thrombo-angiitis obliterans, which term has been generally adopted. His subsequent publication of larger groups of cases have further substantiated these observations. Todyo, in 1912, correlated the work of former investigators and described diffuse vascular inflammation with intimal proliferation and thrombosis of the lumina of the arteries and veins. In the last ten years many cases have been reported in American and foreign literature.

Two hundred cases of thrombo-angiitis obliterans seen and carefully studied at the Mayo Clinic from 1922 to 1926 inclusive, form the basis of this report.*

*Submitted for publication January 24, 1928.

*Three hundred cases will be reported in detail in the form of a monograph at a later date.

Clinical Course

Thrombo-angiitis obliterans, Buerger's disease, or the endarteritis obliterans of Winiwarter, is an obliterative disease of the arteries and veins of the extremities, occurring principally between the ages of twenty-five and forty-five years, and affecting only males, in our experience predominantly Jews, who are excessive smokers of tobacco. The disease first manifests itself by excessive fatigue in the extremities followed shortly by the pain of claudication (brought on by exercise and relieved by rest) which is in turn followed by or associated with marked rubor when the extremities are dependent and excessive pallor when they are elevated. Trophic changes occur either in a minor form, such as excessive callosities in the weight-bearing areas, or in the major form as gangrenous ulcers of the digits or gangrene involving the toes or the entire foot (figs. 1 and 2). Before trophic changes occur, pain is usually absent or mild when the patient is at rest; with the onset of trophic changes rest-pain frequently becomes so se-

Fig. 1. Thrombo-angiitis obliterans of the hands with an unhealed amputation wound of the fourth right digit and a small ulcer on the left thumb.

vere that patients beg for amputation. When the disease is well established the extremities are objectively cold and there is a reddish cyanotic color

ties frequently occurs during the course of the disease and is presumptive evidence of occlusion of the larger veins.

FIG. 2. Thrombo-angiitis obliterans of the right foot with gangrene of the great toe and superficial phlebitis.

of varying degree when they are in the dependent position, and pulsation in the arteries of the feet and legs or upper extremities is diminished or absent. In about 40 per cent of the cases superficial phlebitis is associated at some time during the course of the disease. Edema of the lower extremi-

ETIOLOGY

The etiology of thrombo-angiitis obliterans is unknown. It is Buerger's opinion that the disease is of specific infectious or toxic origin, producing its effect primarily in the walls of the arteries and veins. Rabinowitz iso-

lated an organism from the blood in cases of thrombo-angiitis obliterans with which he produced vascular lesions in rabbits somewhat similar to those observed in man. He described this organism as a gram-negative, aërobic, facultative anaërobic, freely motile bacillus of medium size, beaded, bi-polar in appearance and containing metachromatic granules. Rosenow and Nickel have cultured the veins resected in acute phlebitis with negative results. Meyer (22) believes that the disease is due to excessive tobacco smoking alone and that the vascular changes are secondary to "saturation" with tobacco smoke. Changed viscosity of the blood is thought to be a factor by Koga and Koyano. Goodman and Bernstein thought latent typhus fever was a factor. Steel believed that the coagulation time of the blood was shortened. Ochsner believed that a high-salt diet was a factor, and Chlumsky thought the superficial phlebitis and the cutaneous nodosities were due to fly bites. That syphilis is not a factor has been demonstrated by Perla, Buerger and Kaliski, and by our studies. In our series, increased viscosity or shortened coagulation time of the blood, diet, typhus fever or fly bites did not seem responsible.

Possible Contributory Etiologic Factors

Race.—Although thrombo-angiitis obliterans occurs predominantly in Russian Jews, it has been reported in Swedes by Ochsner; in Chinese by Meleney and Miller, and Whyte; in Japanese by Koyano, and Ito; in Koreans by Ludlow; in Turks by Wieting; and a questionable case has been reported in a negro by Gemmill. In approximately 50 per cent of our cases the patients were Jews, the remainer beings Austrians, Finns, Norwegians, Germans, Scotch, Irish, French, English, Dutch, Greeks, native Americans, and those of mixed ancestry. Although this disease occurs in almost every known race it has a definite predilection for Jews.

Smoking.—Only three patients of this series were total abstainers from tobacco smoking. In a control series of other diseases of cases in which the age was comparable and the sex the same, there were forty patients who did not smoke and the remainder used tobacco less extensively than most of the patients with thrombo-angiitis obliterans. Care must be used in evaluating the tobacco factor as occasionally tobacco smoking is initiated (and usually it is accentuated) after the disease has progressed to the point of causing pain, insomnia and nervousness. However, with full consideration of these factors it is evident that tobacco smoking is much more common in patients with thrombo-angiitis obliterans and may constitute a contributory etiologic factor.

Birthplace.—Eighty-six per cent of the Jews and twenty-four per cent of the Gentiles of this series were foreign born. In the control series of other diseases, 75 per cent of the Jews and 28 per cent of the Gentiles were foreign born. This would indicate that birthplace plays no rôle in thrombo-angiitis obliterans.

Sex.—The occurrence of thrombo-angiitis obliterans exclusively in men has been noted by all authors except Koyano, Meleney and Miller, each of whom report a case occurring in a woman. Buerger reported three cases in women. Pathologic proof was lacking in the cases of Koyano and Buerger. Meleney and Miller found that the dissected vessels were microscopically similar to those observed in thrombo-angiitis obliterans. All patients of our series were males.

Syphilis.—In only 6 (3 per cent) of the cases was the Wassermann test positive. We believe this was due to associated syphilis.

Foci of infection.—In eighty-seven cases of this group the teeth were examined roentgenographically, in 75 per cent of these periapical infection was definite enough to be considered clinically important. In 80 per cent of all the cases the tonsils were enlarged and contained plugs or fluid pus. In forty-six cases the prostate was examined by the method of Von Lackum; in 52 per cent prostatitis was marked enough to be considered of clinical importance. In only three cases of the entire group were there no demonstrable foci of infection. The fact that this disease in our experience occurs exclusively in men leads to the impression that the prostate may serve as an important focus of infection but the theory lacks proof as does the impression that any distant foci of infection are of etiologic significance.

Thermal conditions. — The first symptoms were noted in cold weather in 71 per cent of our cases. It is not known whether cold is an etiologic factor or whether the symptoms are first noticed in cold weather because of increased demand for greater circulation. Cold probably plays a contributory or exciting part.

Occupation.—Eighty per cent of the patients in this series were active workers, such as farmers, blacksmiths, truck-drivers, brakemen, oil workers, foundry workers, boiler-makers, miners, lumber-yard employees, clerks, electricians, pedlers, carpenters, plumbers, engineers, teachers, shoe-makers, barbers, junk-dealers, bakers and sausage-makers. A control group of an equal number of patients with diseases other than thrombo-angiitis obliterans showed the same percentage actively employed. Occupation therefore has no bearing on the cause of the disease.

Age.—All authors have agreed that the limits of incidence lie almost constantly between the ages of twenty-five and fifty. Frauenthal reported a case of bilateral spontaneous gangrene of the hands in a male child, aged three years, which he thought was thrombo-angiitis obliterans, but the data were insufficient for diagnosis. Koyano reported the case of a patient whose symptoms began at the age of nine years. The youngest patient in the present group was seventeen, the oldest sixty-four. In the latter case gangrene and arterial obliteration were present, the history was suggestive of superficial phlebitis, and arteriosclerosis was not demonstrable roentgenographically. The diagnosis was not proved pathologically. The

age grouping in this series was as follows: from fifteen to twenty-five years, six cases; from twenty-five to thirty years, eighteen cases; from thirty to thirty-five years, thirty-one cases; from thirty-five to forty years, thirty-three cases; from forty to forty-five years, thirty-one cases; from forty-five to fifty years, thirty-one cases; from fifty to fifty-five years, fourteen cases; from fifty-five to sixty years, three cases; from sixty to sixty-five years, two cases. In the cases in the seventh decade and in some of the sixth decade the diagnosis was not proved pathologically.

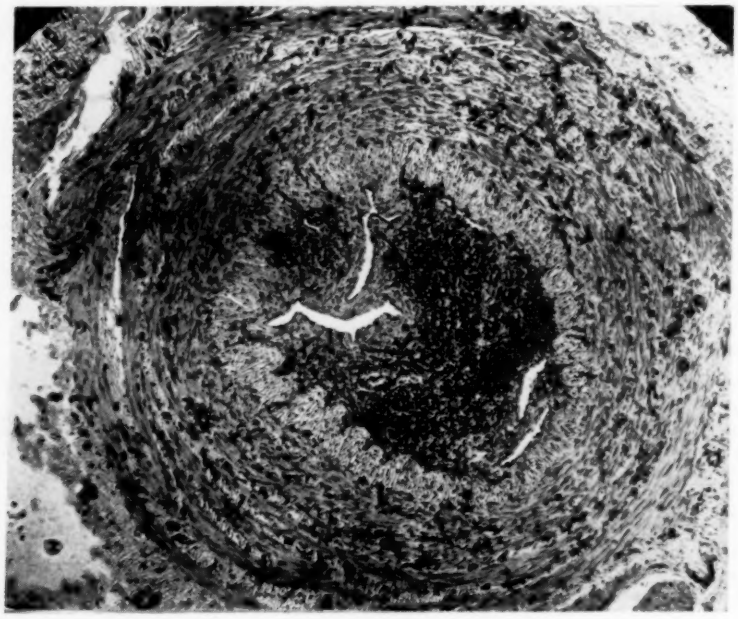

FIG. 3. An artery from a case of thrombo-angiitis obliterans. The lumen is occluded by an organized thrombus which is partly canalized. There is cellular infiltration of the arterial wall and the thrombus.

PATHOLOGY

The earliest pathologic change according to Buerger (7, 8, 9) is a diffuse acute inflammation affecting the walls of the arteries and veins, with secondary thrombosis. The thrombus is composed of erythrocytes, leukocytes, and fibrin. Purulent foci are formed in the periphery in which giant-cells are observed. With subsidence of the acute reaction, fibroblasts migrate into the thrombus and organization takes place (fig. 3). Angioblasts penetrate into the thrombus forming new vascular channels. Eventually the perivascular tissues, the artery and the vein become included in dense fibrous tissue (fig. 4). The capillary channels coalesce and fairly large vessels are formed in the organized thrombus. Elastic tissue and muscle layers are observed in the

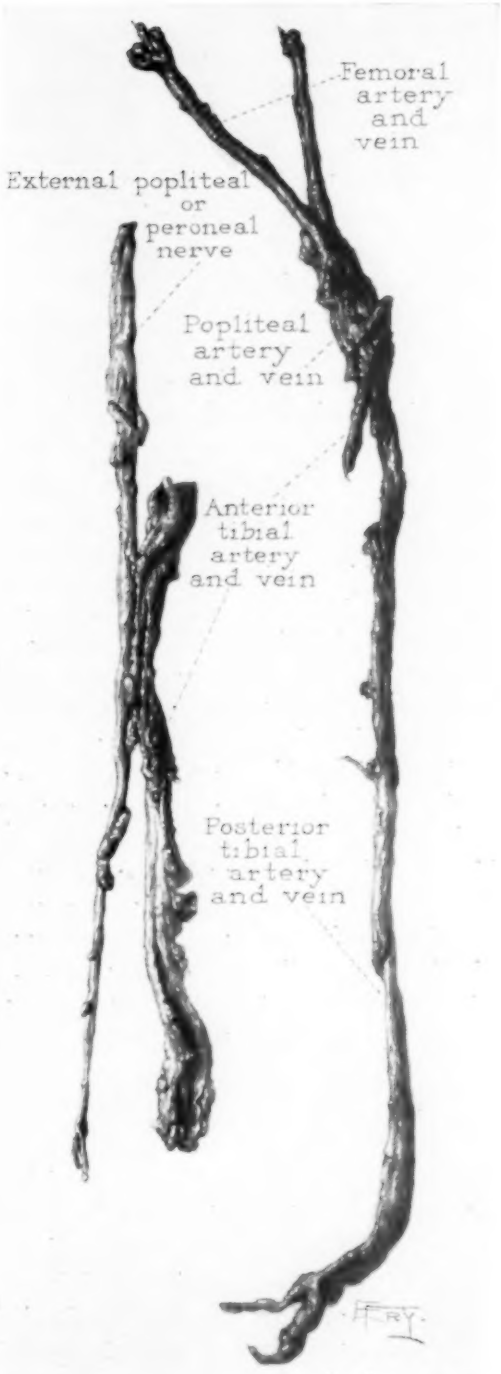
Femoral artery and vein
External popliteal or peroneal nerve
Popliteal artery and vein
Anterior tibial artery and vein
Posterior tibial artery and vein

FIG. 4. Vessels dissected from the leg in a case of thrombo-angiitis obliterans showing the perivascular binding.

walls of the older vascular channels. The evolution of the process can be followed by histologic study of the excised segments of the veins involved in the superficial phlebitis. We have studied thirty amputated limbs and eight resected veins pathologically. Mahorner has studied this same material pathologically to determine if possible the prethrombotic changes in the intima. His observations agree essentially with those of Buerger except in respect to the interpretation of the intimal changes; in his experience evidence of acute inflammation was extremely rare. Mahorner found active intimal proliferation in the arteries and veins which was more marked than is found in control subjects of similar age. He describes projections of the intima with deposition of fibrin and platelets on the summits. There was no thrombosis either distally or proximally to the localized intimitis. The chief difficulty in deciding this point rests on the rarity of specimens at this stage of the disease. Changes in the intima would be anticipated on a priori grounds to account for the deposition of the thrombus, as changes in the blood and circulatory disturbances have not been demonstrated in this disease.

Clinical Types

The following forms of the disease were commonly observed: (1) acute fulminating, (2) slowly progressive, (3) nonprogressive, and (4) compensated or healed. Unusual forms of the disease were: (1) extensive gangrene without pain (1), (2) venous involvement only, (3) normally pulsating arteries (3), (4) vasomotor disturbances suggesting Raynaud's disease (2) (5) associated arteriosclerosis, (6) absence of trophic changes, (7) severe rest-pain without trophic changes, (8) absence of symptoms, (9) onset with suddent vascular occlusion, and (10) onset with edema.

Early Symptoms

Pain of claudication was the first symptom in 51 per cent of the cases in this series. The longest history was fifteen years and the shortest two months. Coldness of the extremities was the first symptom in 12 per cent; the longest duration was four years, the shortest eleven months. Abnormal fatigue was the first symptom in 11 per cent; the longest duration was five years, the shortest four months. Nonhealing ulcer was the first symptom in 10 per cent, the longest duration was six years, the shortest was eight months. Sudden arterial occlusion provoked the first symptom in 7 per cent. Recurrent superficial phlebitis was the earliest symptom in 4 per cent, being of sixteen years' duration in one case. Edema was the first symptom in 3 per cent, and vasomotor disturbances of spastic type only, in 2 per cent.

Differential Diagnosis

We are of the opinion that in no branch of medicine does more confusion exist in the differential diagnosis than in that of the localized vascular diseases. This is mostly because the primary distinction is not drawn between the organic or occlusive diseases and the vasomotor or functional disturb-

ances since color changes (pallor, cyanosis and rubor) may be common to both groups and since they are frequently so striking that they largely overshadow the basic occlusive disturbance. For purposes of orientation, a simple classification of the usual arterial diseases has been proposed by Brown (1, 6). This is not offered as a complete classification but one which according to our experience covers approximately 95 per cent of the clinical types (Table 1). The main division is that between the organic or occlusive and the functional or vasomotor diseases, each of which has a local and a general distribution. Only those of a local distribution will be considered here. We have not included in the classification the syphilitic forms of vascular disease, nor the pathologic rarity, periarteritis nodosa. The organic and vasomotor types can be differentiated in 90 per cent of the cases by determining the state of the pulsations in the palpable arteries of the extremities (Table 2). In 10 per cent of the cases of peripheral vascular disease three particularly confusing types of cases are found: (1) those in which occlusive lesions involve only the distal arteries of the fingers and toes and pulsation in the usual palpable vessels is normal, (2) cases of organic disease with associated vasomotor disturbances simulating Raynaud's disease, and (3) cases of associated arteriosclerotic disease and thrombo-angiitis obliterans.

Two diseases, thrombo-angiitis obliterans and arteriosclerotic disease, make up 95 per cent of the occlusive arterial diseases of localized distribution. They have, in common, arterial obliteration with symptoms of arterial insufficiency (excessive fatigue or the pain of claudication) coldness of the extremities, excessive rubor with dependence and excessive pallor with elevation. The first occurs predominantly in Jews who smoke heavily, in our experience always men, usually between the ages of twenty-five and forty-five, and in about 30 per cent of the cases associated at some time with superficial phlebitis. The rubor of the feet is intense, minor trophic changes are extremely painful and there is usually a moist, inflammatory reaction around them. The arteries cannot be demonstrated roentgenographically. Arteriosclerotic disease occurs in older persons usually between fifty-five and eighty-five and there is evidence of arteriosclerosis in the extremities and elsewhere. There is no racial preference, women are occasionally affected, there is no associated superficial phlebitis, the rubor is usually milder, the ulcers are less painful and usually dry, and there is no inflammatory reaction. Arteriosclerosis can be demonstrated roentgenographically in most cases.

The early diagnosis of thrombo-angiitis obliterans is most essential. This is relatively simple if one considers the underlying basis of the initial symptoms and the impaired supply of blood. Excessive fatigue, if of relatively short duration in the arch, ankle, or calf of the leg, or of the wrist or forearm, should lead to inspection of the arteries of the extremities. Frequently this important symptom and the pain of claudication, both expressions of anoxemia, are

overlooked and the patient is treated for fallen arches, rheumatism or metatarsalgia, or fitted with special shoes which fail to give relief. When the rubor occurs in the digits, deep-seated infection is occasionally diagnosed in spite of the local absence of heat, and toe nails and finger nails are removed or incisions made. In 50 per cent of our cases of gangrene this had been done, and the gangrene thus initiated. When major trophic changes are present, the diagnosis is usually "gangrene." Frequently no attempt is made to determine the cause, as a result of which toes are amputated, healing does not occur and successively higher amputations are necessary.

The vasomotor or functional form of vascular disease of localized nature comprises two types: the vasospastic and vasodilator. These have in common pulsating arteries in the involved extremities, absence of symptoms of arterial insufficiency and lack of marked changes in color with change of posture. The disturbances are intermittent, and in the early stages complete recovery occurs. These data usually serve to differentiate them from the occlusive lesions (thromboangiitis obliterans and arteriosclerotic disease). The vasospastic type includes a large group of conditions variously designated as acrocyanosis and acroasphyxia; when distinct color reactions are present with pain or trophic disturbances of bilateral distribution the condition is correctly designated Raynaud's disease. The fundamental disturbance is similar in all these conditions, consisting of an hyperirritable vasoconstrictor mechanism in the acral areas. The patients conform closely to a constitutional type designated by Müller as "vasoneurotic constitution." Intermittent vasoconstriction of the superficial arterioles, capillaries and veins produces pallor and cessation of the flow of blood in these vessels with depression of superficial temperature. This is followed by dilatation of the skin capillaries with partial resumption of the flow of blood in the capillary loops sufficient to produce dilatation and opening up of the many capillaries but not sufficiently rapid to prevent cyanosis of the capillary blood. The stage of rubor represents a recovery reaction with dilatation of the arterioles and rapid capillary flow with dilated and many open loops; the surface temperature increases.

The vasodilator disorders are characterized by intermittent attacks of burning and redness in the extremities. The feet are hot, the veins dilated, the arteries exhibit excessive pulsations and gangrene does not occur. Many border-line cases are observed. Symptomatic erythromelalgia, that is, burning of the feet without objective evidence of increased surface heat, is frequently associated with arteriosclerosis.

Site of Lesions

Koyano in 125 cases found associated involvement of upper and lower extremities in 30 per cent. In four cases in our series reported by Constam, the symptoms were primarily in the hands, due to obliteration of the radial or ulnar arteries or both. In 60 per cent of the forty cases in our series in which the upper extremities were carefully examined there was

complete or partial closure of the ulnar or radial arteries.

There was no noticeable difference in the frequency of involvement in the right and left extremities. The frequency of involvement of the arteries was as follows: the dorsalis pedis, posterior tibial, popliteal, and femoral in the lower extremities, and the ulnar and radial in the upper extremities.

Laboratory Data

The number of erythrocytes and leukocytes was normal in this group, except in a few cases in which there was marked inflammation around the gangrenous ulcer, usually associated with mild leukocytosis and anemia. The blood sugar and blood urea values were normal. The viscosity of the blood and the platelet count were normal in the few cases so studied. The urine frequently contained a slight amount of albumin, pus, or casts, but these were not considered significant. The phenolsulphonephthalein test for renal function showed nothing abnormal. The cholesterol in the blood by the Bloor I and Bloor II methods in nine cases were at the lower limit of normal and the lecithin and fatty acid were normal in the same cases. Oral temperature and pulse rate were normal except in a few cases of gangrene or secondary infection in which both were slightly increased. The arteries of the extremities could be demonstrated roentgenographically in two cases of this group indicating associated calcification of the media characteristic of arteriosclerotic disease.

Summary

Two hundred cases of thrombo-angiitis obliterans in men have been carefully studied. The pathologic studies were carried out in thirty amputated limbs and eight resected veins, the observations were essentially those described by Buerger except in two regards. The evidence of acute inflammation was extremely rare. Proliferation of the intima was found which seemed out of proportion to the age of the patient. It is felt that these intimal changes may be prethrombotic. Thrombo-angiitis obliterans is apparently a disease of infectious origin. Bacteriologic investigations were made on veins which were clinically acute or subacute but no specific organisms were demonstrated. The diagnosis is relatively simple if the nature of the localized vascular diseases of the extremities is adequately understood.

TABLE I

TENTATIVE CLINICAL CLASSIFICATION OF ARTERIAL DISEASES*

Functional or vasomotor types	Local distribution	Vasoconstricting types	1. Multiple-phase color reaction: Raynaud's disease
			2. One-phase color reaction; acrocyanosis, dead finger, local syncope
		Vasodilating types	Primary erythromelalgia
	General distribution	Vasoconstricting types	Primary or essential hypertension (early stages)
		Vasodilating types	Primary or essential hypotension
Organic types	Local distribution		1. Arteriosclerosis, with or without thrombosis; diabetic gangrene
			2. Thrombo-angiitis obliterans
			3. Arteritis of known infectious origin (rheumatic) (†)
			4. Aneurysm with or without thrombosis
	General distribution		Arteriosclerosis
			1. Primary
			2. Secondary to hypertension

*In our experience, this classification will cover practically all the usual forms of arterial disease.
†A pathologic rather than a clinical entity.

TABLE 2

TABLE 2

DIFFERENTIAL DIAGNOSIS OF VASCULAR DISEASE AFFECTING THE EXTREMITIES

	Thrombo-angiitis obliterans	Arteriosclerotic disease	Raynaud's disease and similar conditions	Primary erythromelalgia
Pulsation of peripheral arteries	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Normal	Normal
Excessive rubor with dependence	Present	Present	Absent	Absent
Excessive pallor with elevation	Present	Present	Absent	Absent
Claudication	Usually present	Usually present	Absent	Absent
Gangrene	Common	Common	Rare	Never
Rest-pain	Usually very severe	Usually mild	Usually absent	Usually mild
Type of rest-pain	Sharp, stinging	Aching	Absent	Burning
Appearance of gangrenous ulcers	Moist, inflamed, discharging	Dry	Small punched-out areas	None
Superficial phlebitis	30 per cent of cases	Absent	Absent	Absent
Age at onset of symptoms	Mostly between twenty-five and forty-five years	Mostly between fifty-five and eighty-five years	Mostly between seventeen and thirty-five years	Mostly between thirty and fifty years
Sex	Males 99 per cent	Males 90 per cent	Females 95 per cent	Females 70 per cent
Race	Hebrews 50 per cent	Any	Any	Any
Roentgenographic appearance of arteries	Usually no sclerosis	Usually sclerosis	Normal	Normal
Color changes following exposure to cold	30 per cent	15 to 20 per cent	Always	Never
Temperature of extremities	Low	Low	Low	High
Edema	Frequent	Infrequent	Absent	Absent

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Thrombo-Angiitis Obliterans: A Clinical Study of 200 Cases*

II. Treatment and Prognosis

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MANY methods of treating thrombo - angiitis obliterans have been suggested. Chief among these from a medical standpoint is the method of administrating sodium chloride solution subcutaneously (Koga) and by stomach tube (McArthur) in order to reduce a supposed increase in the viscosity of the blood; the method of Sinkowitz and Gottlieb for the utilization of the hyperemic method of Bier; the use of diathermy (Wright); the use of white light (Frauenthal); injection of insulin (Ambard, Boyer and Schmid); the intravenous injection of sodium citrate (Steel); and the irradiation of spinal areas (Philips and Tunick). From a surgical standpoint, other than amputation, anastomosis of the femoral artery and vein was carried out by Lilienthal and advocated by Wieting and Meyer. Buerger believed there was a certain type of case in which this was of value, but Oppenheim did not have good results and Stetten collected 136 cases in which the procedure had been attended by a mortality rate of 30 per cent, absolute failure in 72 per cent, and good results in only 11 per cent. Lewis and Reichert reported one case in which benefit followed ligation of the femoral artery. Ginsberg ligated the femoral vein in four cases with slight improvement in one. Silbert injected the nerve in the malleolar region with absolute alcohol; pain was satisfactorily relieved and there were no untoward results. Herzberg analyzed 110 cases of adrenalectomy, fifty-four of which had been observed from six months to two years. The disease was quiescent in eleven, and ameliorated in nine; amputation had been performed in thirty-two. Brown and Rowntree reported the results of periarterial neurectomy, as devised by Leriche, in seventeen cases; they did not find sufficient benefit to justify continuance of the procedure.

There has been an increasing tendency toward conservatism in surgery and prolongation of medical treat-

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ment. This has been justified by a number of facts which have become apparent: (1) pain can be relieved in many cases for a long time by medical measures; (2) in many cases sufficient circulation will be re-established to keep the extremity functionally adequate provided rest or trophic types of pain when present can be relieved; (3) there are many indications that the disease is of a recurrent infectious type, hence attention must be directed to the elimination of foci of infection; (4) with adequate medical treatment amputation can be carried out at a low level in selected cases; (5) lumbar ganglionectomy and ramisection is of value in selected cases, and (6) major trophic changes, such as gangrenous ulcers, are occasionally amenable to medical measures.

Selection of treatment.—The type of lesion must be considered in the treatment; five types can be differentiated:

1. Extensive gangrene with or without pain; the treatment is amputation.

2. Mild trophic changes with severe rest-pain; the treatment consists of medical measures for the relief of pain, methods to increase the circulation, prophylactic measures and removal of foci, lumbar ganglionectomy and ramisection may be carried out in suitable cases. If medical measures for the relief of pain are unsuccessful, amputation is indicated or lumbar ganglionectomy and ramisection may be performed in suitable cases.

3. Mild trophic changes without rest-pain; the treatment consists of prophylactic measures, removal of foci of infection, measures to increase the circulation and lumbar ganglionectomy and ramisection in suitable cases.

4. Severe rest-pain without trophic changes; the treatment is the same as that in the second type.

5. Neither rest-pain nor trophic changes; the treatment consists of prophylactic measures, removal of foci of infection and measures to increase circulation.

The economic factor is worthy of more than cursory consideration in the selection of the type of treatment. Palliative or expectant treatment is frequently uncertain in its results and always a financial burden on patients of slender means. This is well illustrated in the case of a Greek waiter with a ten-year history of thrombo-angiitis obliterans. When the first symptoms began he owned a small restaurant, had money in the bank and was well enough situated to be assured of financial independence. With the first symptoms came disability, idleness in hospital and physicians' fees. The principal in the bank was exhausted, the restaurant mortgaged and later sold and the patient became a waiter, unable to work more than two or three days a week, nor to earn more than a precarious livelihood. In ten years he had spent $10,000 for medical care alone and had spent three years in hospitals. How much better would it have been had amputation been performed when the first symptom appeared! In cases of trophic change or severe pain medical

treatment should not be given unless the patient fully understands the uncertain results and the financial burden involved.

Medical treatment.—Medical treatment should include prophylaxis, measures to increase the local circulation, removal of foci of infection and relief of pain. The extremity should be closely protected from trauma and cold. Care should be used in the treatment of minor abrasions as these may initiate gangrene. Calluses should not be incised nor toe nails trimmed too closely. Woolen socks with felt boots are the best protection from cold. Patients should be instructed to rest the extremities as frequently as their occupation allows. Certain types of occupation must be forbidden. If the patients are of adequate financial means, a period of six months to one year of almost complete rest is of great value. Smoking should be interdicted or sharply diminished.

Routine measures to increase the blood supply of the extremity include the so-called contrast baths, that is, immersing the extremity to the knee for one minute in cold water (from 50 to 60°F.) and quickly changing to warm water (from 102 to 105°F.) for the same length of time. This is repeated fifteen times, at least twice daily ending with the warm bath. Radiant heat from the carbon-filament lamp is applied for increasing periods of time. Great care should be exercised to prevent burning. Postural exercises consist in elevating the feet for one minute, hanging them over the edge of the bed for one minute, and keeping them horizontal for one minute; this is repeated ten times on three occasions daily. Nonspecific protein is used to induce fever. We have demonstrated by calorimetric methods a measurable increase in the volume flow of blood during fever. This is accomplished by vasodilatation of the collateral vessels in the diseased extremity. The relief of pain by this measure is often the most striking, and the beneficial effect of the temporary increase of the blood supply is evidenced by accelerated healing in the trophic ulcers. We have employed typhoid vaccine intravenously, as suggested by Goodman and Gottesman for the artificial production of fever.

The removal of foci is an entirely empiric procedure as there is no evidence to incriminate them etiologically. A study of the pathology of the disease indicates an infectious or toxic basis and we have followed the procedure of eradicating obvious foci of infection in teeth, tonsils, and prostate.

Intravenous injections of radium chloride (2) have temporarily relieved pain in 70 per cent of cases. Equal results are obtained by the injection of triple typhoid vaccine intravenously (10). The latter is cheaper and more readily available. The original injection should contain 15,000,000 to 20,000,000 organisms and be increased by a similar number at each injection. A chill and an increase of from 2 to 4°F. in temperature indicates a satisfactory response. The injection can be repeated four or five times at intervals of three or four days. No bad effects of this treat-

ment have been observed in approximately 6000 injections in cases of thrombo-angiitis obliterans and chronic arthritis. After several injections the reactions may be slight but after two or three weeks without any injections strong reactions will again be produced.

Surgery of the sympathetics.—Lumbar ganglionectomy and ramisection produce definite and persistent vasodilatation of the vessels of the feet when vascular dilatation is obtainable, as demonstrated by Adson and Brown (1, 5). The rationale of the application of this operation in cases of thrombo-angiitis obliterans in which the main vessels are closed is based on two observations: (1) the frequency with which vasoconstrictor intermittent disturbances are observed in this disease as manifested by color changes, such as pallor and cyanosis, which are usually induced by cold, and (2) the quantitative evidence of vasodilatation that occurs in the diseased extremity with increased environmental and body temperature. From these observations, cases of thrombo-angiitis obliterans can be divided into two groups: those with and those without vasomotor spasm of the collateral vessels. A vasodilating type of operation would exert an effect only on the former type of case. The problem consisted in determining the suitable type of case for operation. Following an injection of typhoid vaccine, the oral temperature and that of the feet are noted at fifteen-minute intervals during the periods of chill and fever. When the surface temperature rises to a greater degree than the oral temperature, vasodilatation of the collateral vessels is present (Fig 1). A vasomotor index is obtained by the following calculation: the vasomotor index equals the increase in surface temperature of the foot less the increase in oral temperature, divided by the increase in oral temperature. This indicates a ratio of the amount of vasodilatation to a given rise in the body temperature. Indexes in excess of 1.5 have been considered favorable for operation. Frequently indexes of from 2 to 3 are obtained. Normals show indexes varying from 2 to 10. Fairly comparable increases in the surface temperature of the diseased feet are obtained preoperatively with fever and postoperatively following lumbar ganglionectomy. This question is still under study and the data are at best only approximate.

Surgery of the extremities (3).—The choice of the area for amputation depends on the condition of the vascular supply of the extremities. Fingers can usually be successfully amputated regardless of the amount of obliteration in the ulnar or radial arteries. In this series the disease was never sufficiently extensive to require the amputation of hands or arms. Toes can be successfully amputated in only a small group in which the arteries in the feet are pulsating normally and the skin proximal to the toes is not discolored or edematous. The study of a large group shows that incision of toes or removal of toe nails is never successful and always necessitates higher amputation. Amputation below the knee is successful in 80 per cent of all cases of thrombo-angiitis

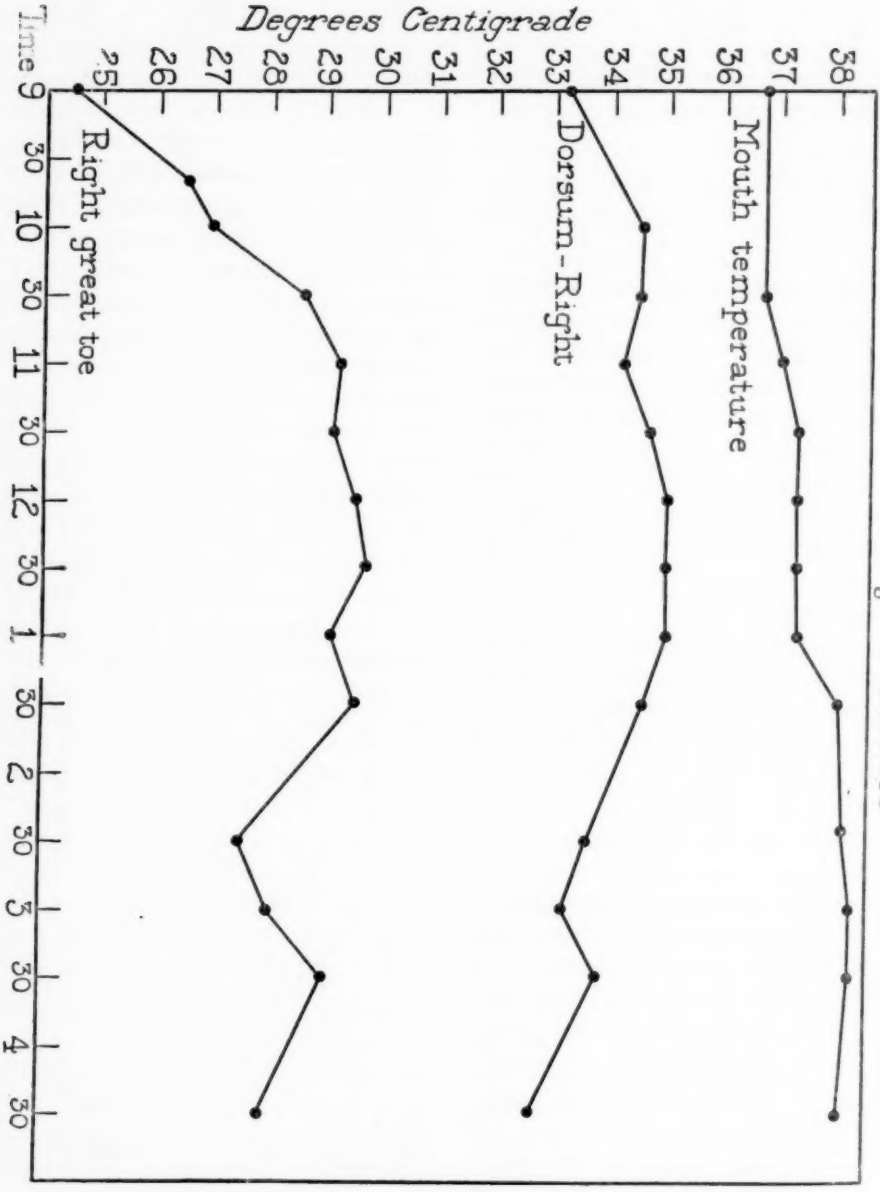

FIG. 1. Foreign protein reaction in thrombo-angiitis obliterans. The skin temperature of the right great toe has increased 3.5°C more than the oral temperature. A comparable increase would probably follow lumbar ganglionectomy.

obliterans regardless of the condition of the pulsations in the popliteal artery provided that the gangrene does not involve the leg and extensive lymph-angiitis or edema is not present. This does not agree with the opinion of other workers who maintain that amputation should always be carried out above the knee. The good result in our series is partially due to the preoperative and postoperative medical care, consisting of the almost continuous application of heat by means of the carbon-filament lamps arranged in an arch over the bed and the intravenous injection of small amounts of foreign protein; both of these measures increase the blood supply of the stump and promote healing. Amputation above the knee should be reserved for cases in which amputation below the knee has been unsuccessful and those in which the patient is unwilling or in too poor physical condition to take the risk of a second operation, if amputation at a lower level has been unsuccessful.

Prognosis

The relation of early recognition to the ultimate outlook of cases of thrombo-angiitis obliterans cannot be too strongly emphasized. The presence of gangrene militates greatly against a favorable prognosis but this can be avoided in a great many cases by the early recognition of the disease and the institution of rational therapeutic methods. This can be brought about by the education of the general practitioner and the orthopedist, who see these cases in their incipiency. Palpation of the usually pulsating arteries, the circulatory efficiency test, and the recognition of symptoms due to an impaired supply of blood will give the clue to the nature of the disease and usually establish the diagnosis in the early stages. The long period between the first symptoms and the occurrence of gangrene, during which time inadequate or irrational treatment is tried, shows plainly how often the first symptoms are misinterpreted.

Thrombo-angiitis obliterans is apparently a self-limiting disease, as the obliterative process eventually stops. The usual clinical course is not that of arterial insufficiency progressing to gangrene but rather that in which arterial obliteration and the establishment of circulation in the old thrombi and by new collateral channels run hand in hand. The new arterial channels increase with time and eventually the limb will obtain a fair degree of arterial compensation. Trophic changes, as gangrene and ulcers, occur in the stage before arterial compensation is established and when present greatly augment the unfavorable prognosis as amputation is required before adequate new circulation is present. Severe rest-pain adds to the dark outlook as medical measures for relief are unsuccessful in many cases and amputation is required. Edema interferes with healing when small ulcers are present and may prompt a decision to amputate at a higher level as good healing does not occur in an edematous limb. The economic factor has much to do with the prognosis. Patients with inadequate means cannot take long periods of medical treatment, and amputation is frequently

the best solution. Patients with similar symptoms but economically better off can have sufficient periods of rest. The following considerations decide a favorable prognosis: (1) early recognition, (2) persistence with rational treatment to increase the circulation, (3) care to avoid all types of trauma, and (4) impressing on the patient the chronic nature of the disease and the need for constant treatment.

Summary

Additional experience with thrombo-angiitis obliterans has tended to favor conservative treatment. Close coöperation of the medical and surgical staff have made possible amputations at a lower level and successful healing of trophic lesions. Amputation has been averted in many cases by carefully and persistently carrying out medical and physical measures for long periods. The control of pain by the injection of foreign proteins, and the induction of vasodilatation, by lumbar ganglionectomy in carefully selected cases, have likewise reduced the number of amputations.

The recognition of this disease in the early stages is of utmost importance, as gangrene and similar serious sequelae can be prevented in a large number of cases when the vascular nature of the disease is understood.

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The Effect of Cholecystectomy On Gastric Acidity*

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MUCH has been written concerning the influence of the various diseases of the gallbladder on gastric acidity, and it has usually been contended that there is a tendency to lowered acid values in such cases. There are many factors, both physiologic and pathologic, that influence gastric acidity. So true is this that at the Mayo Clinic we have come to regard only the extremes in acid values as significant, and even at these we are inclined to look askance. The physiologic variations may be wide, or certain transient unimportant pathologic processes exert a powerful influence on gastric acidity. Migraine frequently is associated with anacidity, and the same is true of unfavorable psychic influence occasioned by the fear of gastric intubation. Unless there is a more or less constant tendency toward one extreme in any pathologic process it is hardly safe to assume that such a disease is exerting an influence on the gastric secretions. Even the time-honored opinion that anacidity is associated with carcinoma of the stomach is open to skepticism. Friedenwald corroborated a statistical study made by one of us (*2*) to the effect that practically half of the lesions of the stomach, proved at operation to be carcinomatous, were found in cases in which free hydrochloric acid was present in varying amounts up to hyperacidity. Clinical records show great variation in free hydrochloric acid values in gallbladder disease. No importance can be placed on this acidity in making a differential diagnosis or in anticipating the intensity of the pathologic change. Diagnostic emphasis has been placed by others on the curve of the fractional analysis in gallbladder disease. It is stated that the curve does not rise but remains low or falls with each succeeding aspiration. This supports the contention of those who maintain that low acid values are significant in gallbladder disease. To our minds the curve of gastric acidity appears to be of no practical value. Extremes in titration values alone are significant. A single aspiration may not reveal this. It is not our purpose in this article, however, to enter into a controversy relative to the value of a single total aspiration as against

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the fractional aspiration as a means of determining the true acid content of the stomach. We wish to report only the effect of cholecystectomy on the acid values. It has been intimated by Rost that cholecystectomy reduces gastric acidity. In speaking of the effects of cholecystectomy he says that there is diminution in the pancreatic secretion, and that "only about one-third of the normal amount of bile plus pancreatic secretion is discharged . . . . This inadequacy of pancreatic and bile secretion in its turn leads to a stasis of food in the duodenum, which reflexly diminishes the hydrochloric acid production in the stomach. This is probably the best explanation for the resulting hydrochloric acid deficiency which now causes numerous general disturbances." De-Takats reports two cases in which lower gastric acids were found after cholecystectomy and cites Hohlweg who reported 83.3 per cent of cases of hypoacidity or anacidity after cholecystectomy. He quotes extensively from the literature and concludes: "The theoretical basis of this procedure (cholecystectomy for hyperacidity) is far from being clear and it is hoped that greater interest in this question may be aroused by this publication." Meyer, Ivy, and McEnery, from experimental work, report, "Our observation, however, would lead us to the view that the removal of the gallbladder per se is not the cause of achylia or anacidity when it occurs."

This study was made in an attempt to prove or disprove by statistical review the impressions regarding the effect of cholecystectomy on gastric acidity. It was decided to compare the gastric acidity before cholecystectomy to that found after the gallbladder had been removed. One hundred consecutive cases with available data were studied. In some instances a single aspiration of the stomach contents comprised the total observation of acid values. In others a fractional analysis was made. When this was done the highest titration available in the series of aspirations was accepted. Thus the highest preoperative values of acidity, whether from fractional or single aspirations, were used and similar readings of postoperative estimations of acid were compared with these. The postoperative analyses were not made shortly after the operation. In some cases the postoperative titrations were carried out two years after the operation. There is a possibility of extreme variations in the curve of any fractional analysis or in single aspirations under circumstances thought to be constant. This instability of gastric titration values must necessarily somewhat limit the usefulness of this report. The average result of a series of cases, however, should be of some value.

The continuous line shown in Chart I represents the curve of the amount of free hydrochloric acid in these 100 cases arranged in sequence of increasing titration values. Each block represents the acid value obtained in one case. The interrupted line represents the tabulations of the postoperative acidity as compared with the preoperative acidity in each case. Every perpendicular column, therefore, includes two readings, one the preoperative acidity and the other

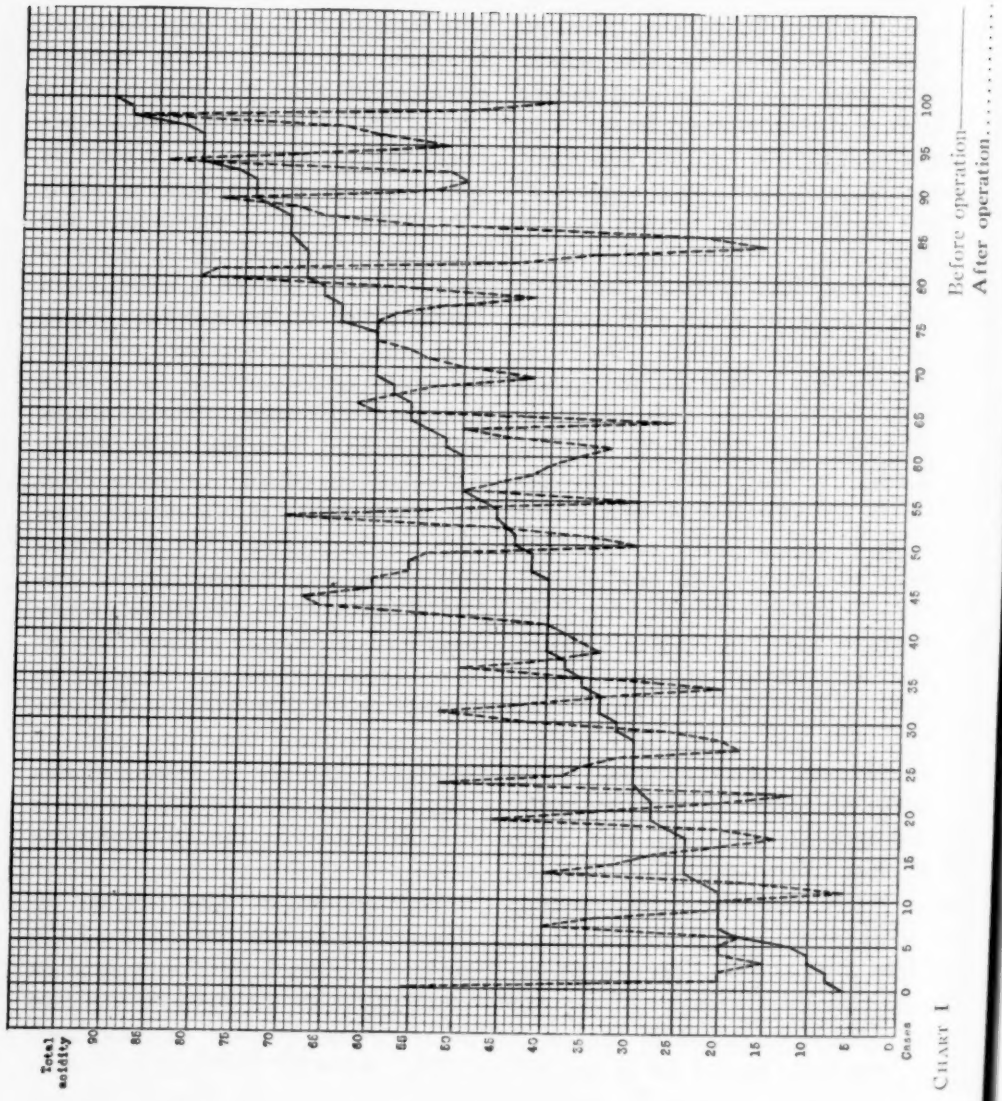

CHART I. Gastric acidity before and after cholecystectomy, arranged according to the increasing acid values of the preoperative acidities.

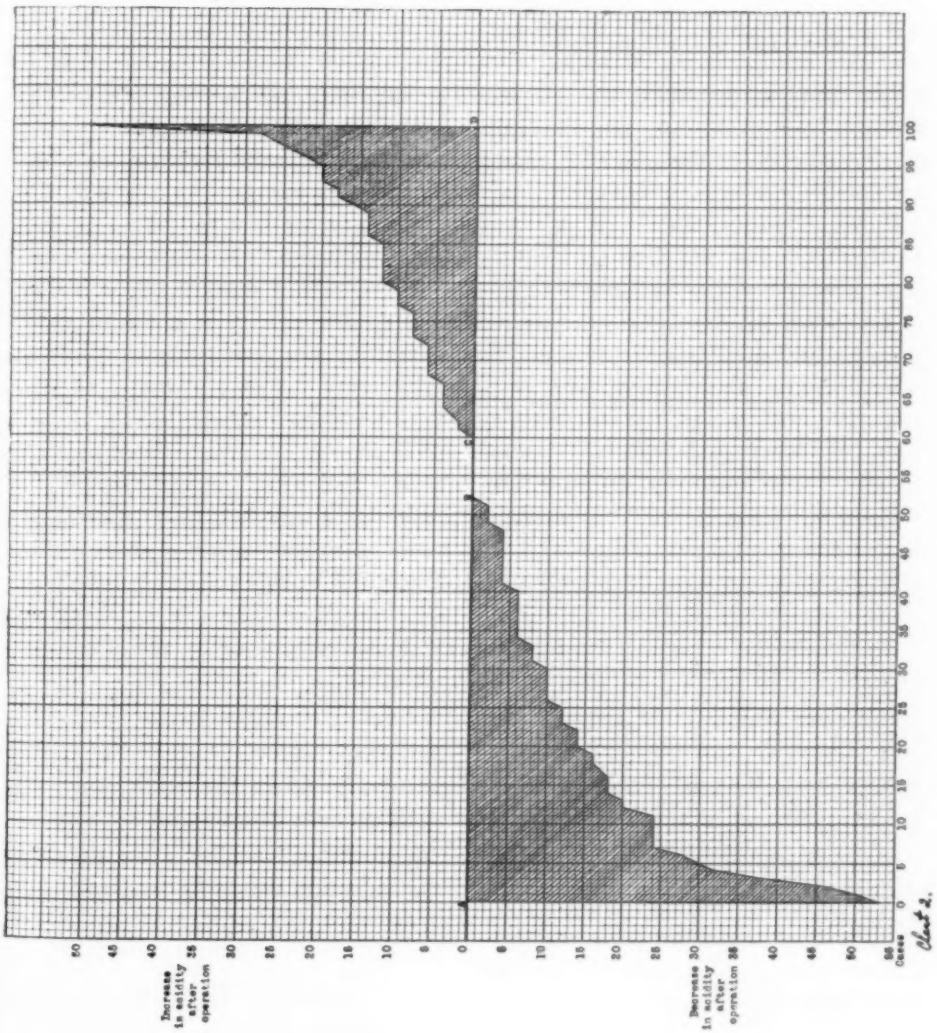

CHART 2. Decrease and increase in gastric acidity after cholecystectomy; shown from a base line.

the acidity obtained some time after the gallbladder has been removed. To illustrate, in the first case the preoperative acidity was 6 and the postoperative acidity was 56. In the second case the preoperative acidity was 8 and the postoperative 20. It has already been mentioned that the conclusion reached is that the acid values are low in cholecystic disease. Chart 1 shows, however, that in 38 per cent of the 100 cases the free acid values were evenly distributed from 6 to 40; in sixty-two the free acid values were evenly distributed from 40 to 90. The difference of preoperative and postoperative acid values, for increased as well as decreased acidity, varied greatly. The maximal decrease was 53 points (Case 84). The maximal increase was 50 points (Case 1). In nine cases values were identical, as is more clearly seen in Chart 2.

In the second grouping the increase or decrease in acid values after cholecystectomy was charted from a base line (Chart 2). In fifty-one cases the acidity was lowered from 2 to 53 points, with an average decrease of 15.1 ± 1.2, represented by the portion of the chart marked A B. In nine cases there were identical values before and after operation as indicated by B C on the chart. In the remaining forty cases, comprising part C B of the chart, there was an increase in the acidity varying from 2 to 50 points, with an average increase of 13.0 ± 1.0. Thus the difference between the average decrease, 15.1, and the average increase, 13.0, is 2.1. The probable error is 1.56. This probable error obliterates the difference.

From such a study it seems obvious that gastric acidity is not consistently altered in any one direction by cholecystectomy. From a study of averages with the probable error, there is no change in the free hydrochloric acid before and after cholecystectomy. It may be concluded that cholecystectomy does not alter gastric acidity. Exception to this statement may logically be taken when it is considered that the postoperative titrations were taken when the patients were still ill following cholecystectomy, and some pathologic process may have been present to affect the acidity, yet with such an even distribution of increased and decreased acidity after operation the objection would be illogical.

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The Embryohormonic Relations of the Pituitary Gland to Mesenchymal Tissues

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THE control which the pituitary exercises over the tissues of mesenchymal origin is no less striking than that which the thyroid exercises over the ectoderm (1). In this article I present the clinical and experimental evidence which supports this thesis.

From the mesenchyma are derived the following tissues:

1. Connective tissue.
   (a) Bone.
   (b) Cartilage.
   (c) Dentin and cementin of teeth.
2. Lymph glands.
3. Spleen.
4. Blood vessels.
5. Blood.
6. Fat cells.
7. Smooth muscle.
8. Renal cells.
9. Suprarenal cortex.

It is to be emphasized that the pituitary gland itself is not derived from the mesoderm but is an etodermal tissue and as such is influenced by the thyroid gland which has a selective action on ectodermal tissues (1).

Calling to mind the tissues of mesenchymal origin, it is easy to understand the symptomatology of pituitary disease. Proof of this selective action will go far toward the understanding of endocrine relationships and the interpretation of diseases involving signs and symptoms which arise from the mesenchymal tissues.

We will now discuss seriatim, the tissues involved in pituitary disease. It is quite obvious that all the data concerning each individual tissue cannot be submitted in a single article. Hypopituitarism exemplifying hypopituitary function, serves the purpose of illustrating mesenchymal tissue relationships. The earlier in life this hypopituitarism manifests iself, the more marked is the mesenchymal tissue involvement and the greater its non-development. Some of the mesenchymal tissues are involved to a greater degree than others, bearing the brunt of the effect. As previously emphasized this can be understood on a basis of constitutional inheritance characteristics. (1)

Degenerative changes with hypofunction will uniformly be found in the mesenchymal tissues in hypopituitary states.

Connective Tissue.—In hypopituitarism the connective tissue is not well developed. This condition is

well-known in the Froehlich type of hypopituitarism.

Bone and Cartilage.—Beck (2) says that one of the important functions of the pituitary gland is to stimulate connective tissue growth, especially that of bone. Hypophyseal insufficiency, therefore, leads to undergrowth and defective skeletal development. X-ray studies of the terminal phalanges generally show persistent epiphyseal lines. These marked changes in the osseous and cartilage systems in pituitary insufficiency early in life frequently results in dwarfism. The development of the bone nuclei is markedly delayed. Because of this relationship of the pituitary and bone development, it is natural to assume a pituitary etiology for many bone diseases. Osteogenesis imperfecta is believed by some to be due to pituitary insufficiency. Bauer (3) studying the changes in osteogenesis imperfecta, noted that all mesenchymal tissues, such as bone, cartilage, blood vessels and hematopoietic organs were affected. Chondrodystrophy and the progressive muscular dystrophies are other examples of affections limited to mesodermal structures, Bauer (4a) believes that a constitutional anomaly is usually present in these diseases explaining in this way that infantile hypopituitarism does not give the characteristic picture of an idiopathic bone fragility. Denker (5) believes that the bone changes in otosclerosis are due to pituitary disturbance. It will be remembered as noted in the previous article that the mesodermal bony labryinth surrounds the epithelium of the labryinth.

Keith (6) believes that the anterior lobe of the pituitary renders osteoblasts hypersensitive to the various stresses which fall on the human skeleton during life. It is interesting to speculate concerning the influence exerted by the pituitary on racial characteristics, particularly the osseous development in racial pygmies and giants.

In the later stages of the growing period growth may suddenly become arrested and the infantile changes are permanent, the epiphyses remain ununited and so the long bones are underdeveloped.

The larynx also does not mature, males having and retaining a puerile type of voice.

The influence of the pituitary on bone and cartilage development is generally accepted and unquestioned.

Dentin and Cementin of Teeth.—The dentin and cementin of the teeth are poorly developed or not at all present. Engelbach and Tierney (7) have emphasized these changes in the dentin and cementin. Ridging and hollowing are frequent.

Experimentally induced hypopituitarism in young dogs produces a persistent first dentition. Bauer (4b). Wheelon (8) discusses at length hereditary and endocrine influences on the congenital absence of the upper lateral incisor teeth. The first two cases were apparently hypopituitary, the third hyperpituitary with widely spaced teeth and absent lateral incisors but from the evidence Wheelon presents, this case shows signs of a lessened pituitary function, (loss of libido, weakness). He concludes that

apparently congenital defects of the upper lateral incisor teeth are rather common.

In Simmond's disease (cachexia hypophyseopriva) loss of teeth is very frequent.

Lymph Glands.—The lymph glands are small and hypoplastic in hypopituitarism. The hypoplastic lymph glands are no doubt related to the hypoplasia of the whole hematopoietic system (bone, spleen, blood vessels etc.) The hypopituitary individual not infrequently has enlarged lymph glands with "exhaustion centers" in the lymph nodes.

Spleen.—As previously mentioned the spleen partakes in the hypoplasia of the hematopoietic system. Falta (9a) describes the small spleen seen in pituitary insufficiency.

Blood Vessels.—The blood vessels are hypoplastic in hypopituitarism. This applies to all three coats. These individuals bruise very easily, slight injury such as a slap on the arm, produces a hematoma.

The work of Krogh (10) is of interest in this connection. From experiments on frogs, he suggests that the normal function of the pituitary hormone is to maintain the capillary tonus. This work emphasizes the position he took with Harrop and Rehberg (11) that the pituitary constantly secretes a substance which circulates in a low concentration and maintains the tonicity of the capillaries. This is important in relation to hypertension, arteriosclerosis, arteritis and other blood vessel disturbances.

Hypotension is the rule in hypopituitarism. Bloch (12) assumes from data at hand, and from therapeutic results with pituitary extract that endarteritis obliterans is caused by lack of pituitary substance.

Kopf (13) found in three patients with Raynaud's disease that injections of "hypophysin" resulted in almost immediate relief of the cyanosis.

Pribram (14) found an enlarged sella turcica in Raynaud's disease. Pituitary preparations were used with marked success and it was deemed probable that pituitary extract exerts a regulating influence upon blood vessel tone.

It has been demonstrated by Weed (15) that the pia-arachnoid (blood vessels) is developed from the mesenchyma and its importance in the formation of cerebro-spinal fluid has been established. Weed and Cushing (16) show that pituitary extract produces an increase of cerebro-spinal fluid. Use of this fact has been made clinically for the relief of lumbar puncture headache.

Cassirer (17) cites a list of observations of coincident Raynaud's and pituitary disease. Henius (18) noted the disappearance of capillary spasm following the use of pituitary treatment in a case of pituitary tumor with Raynaud's disease. Bloch (12) cites a case of Raynaud's disease with pituitary involvement which was benefited by pituitary injections. He believes that all cases of Raynaud's disease should receive pituitary injections.

Blood.—If the blood as a whole is related to the state of the pituitary, then hypopituitarism should result in a lessened blood volume and a lessening of the blood elements.

Brown and Keith (19) conclude that the circulating blood and plasma volumes, when compared to body weight are smaller in obese, (hypopituitary)?, than in normal persons. The fat metabolism is slowed through lack of pituitary secretion and therefore the hypopituitary individual *stores* his fat instead of burning it up. Reference is made here to the fact that the fat cells are mesenchymal in origin and intimately linked with the state of the pituitary gland. The obesity of hypopituitary individuals is well-known. Collins and Baudot (20) from their work on the guinea pig, believe that if the conditions described are found in other animals, we may conclude that the embryonic pituitary has a hematopoietic function. Watrin (21) found erythropoietic centers in the pituitary of the pregnant guinea pig and he concludes that other conditions than gestation give rise to erythropoietic centers in the pituitary.

It is natural to infer that the pituitary should influence the blood if we note its relation to bone-marrow. The reticulo-endothelial cells are mesenchymal in origin and for this reason the relation of the pituitary to these cells is very important. Cholesterol injected into the blood stream is taken up by the reticulo-endothelial cells. Such cells, called by Aschoff (22), pseudoxanthoma cells, appear with disturbed fat metabolism, as in lipemia, diabetes, icterus, xanthelasma and chronic cholecystitis, and suggest a normal part played by the reticulo-endothelial system in fat metabolism. I mention here, this relation of reticulo-endothelial system to blood formation and fat metabolism in order to emphasize the intimate association of all mesenchymal elements. Ainslee and I (23) have shown that injections of posterior pituitary extract into rabbits over a course of ten days increases the blood cholesterol approximately thirty per cent, again showing the relation of the pituitary to lipoidemia.

"The circulating blood contains cholesterol esters in the plasma, while the sterol itself is present in the red corpuscles. Here it is assumed to protect the erythrocytes against the action of hemolytic substances which unless counteracted, might tend to cause anemia through excessive hemolysis" (24).

Cholesterol is believed to be concerned in various immunologic reactions though its functions therein cannot at present be defined. McNee and Prusik (25) have shown that the Kupffer cells (reticulo-endothelial) and not the liver parenchyma manufacture bile pigments.

Injections of posterior pituitary extract increase the coagulation of the blood, and the non-coaguability of the blood in hemophilia is decreased by this extract in vitro, whereas anterior lobe extract has the opposite effect, (26-27). This may be, however, a tissue coagulin effect.

Hypopituitary individuals are anemic. This is agreed upon by most authors, (Falta, (9b), Biedl, (28),

Bauer, (4c) and many others). These are the "pasty" looking individuals whose appearance probably results from a combination of blood, lymphatic and obesity factors.

Fat Cells.—Hypopituitary states result in a lessened metabolism with consequent increased deposition. Experimentally induced hypopituitarism also results in lessened fat metabolism with increased fat development.

The thought suggests itself that an increased pituitary secretion over a period of time would result in increased blood cholesterol and may be an etiologic factor in diseases involving cholesterol metabolism. Ainslee and I (29) have attempted to show that diseases involving cholesterol metabolism such as diabetes mellitus, atherosclerosis, certain types of nephritis, cholelithiasis and others, have important relations to states of pituitary hyperfunction and exhaustion.

Coope and Chamberlain (30) found that injections of posterior lobe extracts (using rabbits and rats) is followed by a well-marked increase in the amount of fatty acid in the liver.

Raab (31) found that the high blood fat of starving dogs was reduced through injections of "pituitrin" and pituglandol." This shows that the pituitary aids the cells in utilizing fat.

Smooth Muscle.—Perhaps the easiest way to show the selective action of pituitary secretion on smooth muscle is through the pharmacologic action of posterior lobe injections. This is such a well-known action that everyone is familiar with it. I need but mention the contractile effect it has on the smooth muscle of the uterus, bladder and intestines. Zondek (32) found that posterior lobe extract after a preliminary inhibition, caused increased peristalsis of the intestine. He believes that the posterior lobe secretion exerts a regulatory effect on peristalsis. Consequently in hypopituitarism it would be expected that the tonus of the smooth muscle would be diminished. Abel (33) isolated a very pure tartrate from the pituitary which is from 1000-1250 times stronger than acid histaminphosphate. This affects the smooth muscle in very great dilutions.

Renal Cells.—Hypopituitarism results in polyuria and not infrequently produces diabetes insipidus. That posterior pituitary extract has an effect on renal cells is well-known. Whether this is a diuretic effect or antidiuretic is not yet settled. No doubt dosage, purity of the product, the state of the renal cells, and other factors account for the differences. The concern here is that the renal cells are affected by pituitary secretion.

In diabetes insipidus posterior lobe extract has an antidiuretic effect if lessening of the urinary output is assumed as showing this. An apparently paradoxical situation is present. If the pituitary hormone is essential for proper renal function, then its lack, such as in diabetes insipidus, would result in renal cell hypofunction with water and mineral salt loss. These are essential to body economy. Injection of the hormone stimulates the renal cells to activity with a consequent retention of water and minerals, in other words antidiuresis is

produced. That the action of posterior extract is on the renal epithelium and independent of the systolic pressure has been proven by Hoskins and Means (34).

Skubiszewski (35) studying the micro-physiology of the pituitary in connection with polyuria, in parenchymatus idiopathic nephritis, came to the conclusion that the polyuria may be referred to the pituitary. There is a relation between an increase of basophil leucocytes with deep penetration in the posterior lobe of the pituitary and hyperfunction of these cells. He believes that hyperfunction of the pituitary is responsible for the polyuria. It might also be due to the failure of the tubules to concentrate the urine and this again might be a result of pituitary depression. Falta (9e) says that the polyuria may be referred to a temporary irritation of the posterior lobe through a growing adenoma of the anterior lobe. This conception, he says, may explain the fact that such polyurias also frequently occur in tumors of the hypophysis of other sorts that are associated not with phenomena of hyperfunction of the hypophysis but on the contrary with those of insufficiency. It is evident that polyuria is found in hypo and hyperpituitarism.

Berblinger (36) studying the pituitary in nephritis found a distinct increase of basophil cells in the pituitary in 66.7 per cent of nephritics and an appreciable increase in 31.1 per cent. Hoeppli (37) also verified this basophilic increase. This may be an effort toward compensatory hypertrophy.

Jungmann and Zondek (38) believe that in the condition known as habitual oliguria, the pituitary gland plays a leading role.

The concentration of chlorides in the urine is greater while pituitary extract exerts its effect; this effect is primarily renal, changes in the blood are secondary, (Fromherz (39).)

McFarlane (40) believes that the pituitary accelerates resorption from the tubules by direct action on tubular cells and not by any vascular change.

Starling and Verney (41) found that in dogs, posterior extract, through its action on the kidney, produces an increase of chloride excretion and a decreased water output. Noguchi (42) experimenting with frogs also found this to be true.

Biedl (28) quoted Ide to the effect that the pituitary is an older sister of the genito-urinary apparatus. It has been shown that apituitarism is associated with aplasia of the suprarenal cortex and mal-development of the genito-urinary tract.

Lathrop (43) reports a case of renal dwarfism in which there was a marked retardation of development of the epiphyses, especially at the wrist. The kidneys were both distorted pieces of tissue which externally hardly resembled kidneys. No mention is made of the state of the pituitary. Some of the symptoms while possibly due to the malfunction of the kidneys, are suspiciously like hypofunction of the pituitary, viz. late onset of menstruation, no secondary sex characteristics, polydipsia, polyuria, dwarfism, retardation of ossification. Even the drowsiness, while most likely renal in origin, is like pituitary narcolepsy.

Freund (44) has reported a case of brain tumor in the region of the pituitary, that had a very high blood nitrogen, (270 mgm.) At autopsy no kidney lesion was found. This case illustrates the fact that depressed tubule function might be expected to result from interference with pituitary function.

**Suprarenal Cortex.*—The suprarenal cortex is developed from the coelomic epithelium of the mesoderm in contrast to the medullary portion which has its origin in the sympathochromaphil tissue of the ectoderm.

In hypoplastic states of the pituitary, hypoplasia of the suprarenals is found. Total aplasia of the suprarenals is found in anencephaly, hemicephaly, and other failure of brain development. Ziegler (45) cites several cases of anencephaly and hemicephaly associated with aplasia of the suprarenals. Zander (46) noted that the suprarenals were hypoplastic only in defects of the anterior portion of the brain. This is because the anterior cerebral defects include the pituitary gland, which would, therefore, account for the suprarenal defect.

Why would there be any difference between anterior and posterior brain defects?

Kohn (47) believes that the suprarenal hypophlasia is secondary to changes in the pituitary. Defects are found in the infundibulum and pars nervosa. The epithelial portion also shows changes. There is scarcity of oxyphil and large basophil cells.

Browne (48) studied five anencephalic fetuses. He was struck by the constancy with which the thymus, suprarenals and ovaries were involved in association with the anencephaly. Commenting on Browne's work an editorial in the British Medical Journal (1920, 2, 828) says: "The most rigorous search on the basis cranii of his anencephalic fetuses showed absolutely no trace of a pituitary gland. The syndrome consisting of protruding tongue and eyeballs, nasal aquilinity, obesity, thymus hyperplasia, supprarenal and genital hypoplasia and stunted growth of body and limbs, agrees in the main with the features of what are called hypopituitarism and apituitarism." (See also in this connection Niemann's Disease, Christian's Syndrome, Paget's Disease of the skull, etc.)

Barlow (49) from his study of four anencephalic fetuses could not verify the absence of the pituitary. It must be noted however that apituitarism is present when the anterior portion of the brain is involved. In Zanders 43 cases of anencephaly the suprarenal defect was present only in those cases which include the anterior portion of the brain. We may conclude that in those cases of anencephaly which include the pituitary gland these are the ones in which the suprarenal cortex is hypoplastic. It is apparent that some anencephalics do not have apituitarism and therefore do not show the syndrome completely. Barlow's four cases were probably of this type.

*Some of the remarks on the suprarenal cortex are taken from a previous article.

Moehlig, R. C. The Selective Action of the Suprarenal Cortex Secretion on Mesothelial Tissues. Am. J. Med. Sc. 168, Oct. 553-565, 1924.

Covell (50) whose work was done on 32 fetuses summarizes from his studies as follows:

1. An hypophysis is present in anencephalic fetuses.

2. It is extremely variable in weight. If the weight is corrected for vascularity, it is usually less than the weight of the normal fetal hypophysis which has also been corrected.

3. The pars nervosa is lacking in the majority of cases. When present its relative and absolute volumes are considerably less than those of the normal.

4. The pars intermedia is variable in both occurrence and volume.

No mention is made of the state of the suprarenals and this is of prime importance in the matter under discussion.

Ballantyne (51) described 45 anencephalic fetuses and states that the pituitary rarely occurs. Schwalbe (52), Haberfeld (53), and Wrete (54) found the pituitary to be present. Mausch (55) also found it to be present but abnormal, some of the pituitaries consisting only of two lobes.

Bauer (4d) says that it is still undecided whether the brain development suffers because of suprarenal non-development with consequent lack of lipoid substance for brain development or whether as Zander maintains with Thomas, that the anterior portion of the brain is essential for suprarenal development. My position is that the anterior part of the brain involves the pituitary with the resulting suprarenal involvement.

The pituitary and suprarenal cortex relationship is important because both are of prime importance in lipoid metabolism.

We may conclude that in anencephaly there is a varying amount of pituitary pathology which is often associated with concomitant suprarenal cortex involvement. In the following paper of this series, the suprarenal cortex will be shown to have selective action on mesothelial tissues of which the sex glands and skeletal muscles are important components. It will be readily understood from this that pituitary hypoplasia with suprarenal hypoplasia would result in sex gland and skeletal muscle hypofunction. This is well borne out clinically in pituitary insufficiency with the well marked sexual underdevelopment and muscular fatigue.

Hyperpituitarism and the Mesenchymal Tissues. — The mesenchymal tissues show evidence of increased activity in hyperpituitarism. It is emphasized that not all the evidence which favors the selective action of the pituitary on these tissues will be submitted. This would merely be a monotonous repetition.

Connective Tissue.—The connective tissue in hyperpituitarism is definitely decreased. Connective tissue increase in the internal organs is found in acromegaly. Small and large fibromas and warts are frequently seen in acromegaly (Bauer, 4e). The combination of acromegaly with Von Recklinghausen's neurofibromatosis is seen very frequently.

Bone.—Everyone is familiar with the increased bone deposition present

in hyperpituitarism. The bone changes in gigantism and acromegaly which form such an important part of the clinical picture are examples. The sites for the muscle insertions are also enlarged. The skull, jaw, breast, spine, pelvis and extremities partake of the bone changes. Bassoe (56) gives the skeletal changes in detail. The characteristic spade hand due to phalangeal changes is also a feature of hyperpituitarism.

Cartilage.—Marked changes in cartilage formation of a hyperactive nature are the rule. Due to the cartilaginous overgrowth of the larnyx, the voice becomes very deep and resonant; this is also true of the female. Zondek (57) cites a case of a woman whose voice was soprano before the onset of acromegaly and became a bass voice after the onset. Jackson (58) gives a detailed description of the laryngoscopic appearances in four acromegalic individuals. The cartilages of the ears, nose and ribs also enlarge. Achondroplasia is probably associated with pituitary disturbance.

Dentin and Cementin of Teeth.—In hyperpituitarism the dentin and cementin of the teeth is very well developed. Engelbach and Tierney (7) emphasize the development of the dentin and cementin of the teeth in hyperpituitarism.

Lymph Glands.—General lymphoid hyperplasia is found in hyperpituitarism. Bauer (4f) is inclined to ascribe the lymphocytosis and eosinophilia of hyperpituitarism to the pituitary. He cites an operative case of acromegaly with 7,300 leucocytes, 44 per cent lymphocytes and 17 per cent eosinophiles. Well pronounced status lymphaticus as found in several autopsies is reported. Goldstein (59) reports a case of acromegaly with lymphatic leukaemia in which there was splenomegaly with lymphomegaly.

Spleen.—The spleen is enlarged presenting a definite hyperplasia. Falta (9c) says that the enlargement of the spleen is a partial manifestation of the enlargement of the lymphatic apparatus. In fact the whole reticulo-endothelial system shows evidence of hyperactivity.

Blood Vessels.—There is an unanimous opinion among writers concerning the state of the blood vessels in hyperpituitarism, especially in acromegaly. Arteriosclerosis is one of the earliest changes noted in acromegaly. Earlier authors (Klebs, 60; Brooks 60) lay great stress on the changes in the blood vessels which they maintain are among the earliest observed. Bassoe (61) states that there is a general dilatation of the blood vessels with sclerotic changes. Falta (9c) finds that the vascular system in the later stages of acromegaly almost always show changes. A slight grade of arteriosclerosis develops. Microscopical examination shows that the three vascular coats are involved in these changes and that the media becomes poor in muscle fibers. Borchardt (62) also reports arteriosclerosis as a constant change with likewise increased blood pressure often to 200 mm. Hg. or more. Bauer (4c) reports arteriosclerosis. Cholesterinemia is found in nondiabetic as well as diabetic arteritis and in hypertension. Reference is

again made to the previous article on the pituitary and cholesterol metabolism in which this is discussed more in detail, (23).

Blood.—In hyperpituitarism an increased blood volume is frequently found. Bassoe (53) says that the blood is often found at necropsy to be increased in quantity. Polycythemia may occur. Certainly in the *early* stages of hyperpituitarism increased blood volume would be expected. One is reminded of the large built individuals of hyperpituitary build who are plethoric, with florid complexion and are candidates for nephritis, hypertension, diabetes and their resulting complications. The cosinophilia that is present in hyperpituitarism is especially interesting. This finding, together with the lymphocytosis is reported frequently.

Fat Cells. — From a theoretical standpoint, the fat metabolism would be increased. Hypercholesterinemia is reported. That the pituitary is related to carbohydrate metabolism is well-known and likewise the glycosuria with lessened tolerance in hyperpituitarism is also a well-known clinical fact. Time will not permit further discussion of this important relationship and it is of course so evident that further data for the present purpose is not necessary. The embryonic origin of the islands of Langerhans is not agreed upon. While some state it is mesenchymal in origin, the disagreement does not permit me to include it in the mesenchymal tissues. If true, this would be a most interesting relationship and would help clear up many points in carbohydrate metabolism.

Smooth Muscle. — That fibroids (smooth muscle overgrowth of uterus) are very common in hyperpituitarism, is well-known. Smooth muscle overgrowth of the intestines and bladder is reported.

Renal Cells.—In hyperpituitarism the renal function should be increased and likewise the kidneys themselves should be enlarged. So it is found clinically. (Falta, 9d.) It is rather tempting to associate an increased posterior pituitary secretion which has existed for sometime with certain types of nephritis. Likewise through its action on blood vessels it may be considered in an etiological role in hypertension.

Draper's work (64) on the human constitution is definitely confirmatory of the selective action of pituitary secretion. Of hypertension patients he says that the changes or increases in the bony skeleton are precisely along the line of increase found in acromegaly or gigantism. Women of a certain constitutional type, whose skulls, mandibles and skeletons display the insignia of a previously increased activity of the pituitary gland, may under the specific stimulus of pregnancy, develop hypertension or nephritis, either transient or permanent. The closeness of the two groups (hypertension - nephritis) in morphological characters and their approximation to the combined hypertension-nephritis series suggest that idiopathic hypertension and some types of nephritis are different expressions of one and the same disease. The interesting fact noted in Draper's remarks is that the three tissues concerned, viz. bone, re-

nal cells and blood vessels, are mesenchymal in origin and it is not surprising that the bone changes in the hypertension-nephritis groups were precisely along the line of increase found in hyperpituitarism.

Suprarenal Cortex.—In hyperpituitarism we should find, theoretically, a suprarenal cortex hyperplasia. This is borne out clinically and the association of hyperpituitarism with suprarenal cortex hyperplasia is reported so frequently that it is a generally accepted fact. Falta (9f) says that there is apparently, frequently hyperplasia of the suprarenal cortex. Bassoe, (65) quoting Amsler, Ausch, Eltester and Schroeder, and others, says that the suprarenals have often been enlarged at necropsy. This enlargement is usually confined to the cortex.

Hofstätter (66) found that posterior pituitary extract injections produce suprarenal cortex hypertrophy.

Assuming that there is a suprarenal cortex hyperplasia in hyperpituitarism, then tissues influenced by the cortex would show signs of hyperfunction. As previously mentioned, these tissues for present purposes are the sex glands and skeletal muscle system. In the early stages of acromegaly, the sex gland function is increased, likewise the skeletal muscles are very large, being commensurate with the large bones. The latter condition shows how well functional changes are correlated in allied tissues for the large heavy bones require large muscles to control them. Engelbach and Tierney (7) say that these individuals have unusual muscle strength and attain it without exercise.

In the discussion of the embryohormonic relations of the suprarenal cortex which will be given in the next communication, it will be shown how intimate the relation is between the mesenchyme and mesothelium.

Conclusions

1. The pituitary gland secretion has a selective action on mesenchymal tissues.

2. The suprarenal cortex as a mesenchymal tissue reflects the state of the pituitary gland.

3. Mesothelial tissues, influenced by the suprarenal cortex are likewise influenced by the pituitary gland.

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The Nature of the Primary Renal Lesion Produced by Lead*

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Introduction

THE work was undertaken for the purpose of determining: (1) The appearance of early pathologic-histological lesions caused by lead carbonate in the guinea pig kidney, (2) The quantity of lead carbonate required to produce demonstrable lesions, and (3) The length of time required for the appearance of these changes.

This investigation was thought necessary, because, as will be seen from the literature, there is a large number of authors, whom I put in the second group, who state that the primary renal lesions in lead poisoning are vascular, and only a few authors (Von Leyden, Legge and Goadby) of this group mention parenchymatous changes as being rare and secondary in importance.

Material and Methods

The material used in this study consisted of forty guinea pig (cavia cobaya) kidneys. Of these thirty-six were poisoned with lead, while the remaining four were used as controls for fatty degenerative infiltration. The youngest animal was five months old when it entered the experiment, the age of the other older pigs was not exactly known to us. The animals were kept in as nearly perfect hygienic conditions as possible; fresh drinking water was given each day; food consisted of oats, carrots, cabbage, lettuce, and green hay alternately.

The lead carbonate was given per os in small gelatine capsules in varying doses for different series of animals. Some of the animal series and some individual animals, which survived a longer time, passed through the various dosages, some even through all dosages. The beginning dose was 0.03306 gram, followed by gradually increasing doses: 0.03637, 0.06309, 0,075945 and 0.0909 gram. It must be kept in mind that lead probably gives rise to kidney disease only when ingested continuously for a long time; naturally, of course, in doses which are not sufficient to cause death.

The kidneys were removed as soon as the animal died or in other cases several hours after the death. The kidneys were fixed in mercuric chlorid or Zenker's solution for general histological changes, in 10 per cent

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formalin for fat staining, and in absolute alcohol for glycogen for which Best's carmin method was used. The mercuric chlorid fixed sections were stained with haematoxylin and eosin, and fat was stained with Scharlach-R counterstained with haematoxylin, others with osmic acid.

General Considerations

It is very important to emphasize that laboratory animals should be kept in as nearly perfect hygienic conditions as possible. They should have clean quarters, fresh air and sunshine in so far as possible. Fresh water and food should be at the animals' disposal at all times. The food should be so varied as to produce a balanced menu. This the experimental worker should always bear in mind, as it is essential to keep the animals in perfect health. The stock animals should be treated in the same way, because, if not, they are latently ill before the starting of the experiments, and so give erroneous results. Because the animals were not kept in hygienic conditions, some authors have reported pathological findings as occurring in normal, healthy animals. Animals, which show pathological conditions should not be regarded as normal, and experiments should not be carried out on such animals.

A review of the literature on nephritis saturnina and early renal lesions in lead poisoning precedes the account of our own results.

Literature

Literature on the pathological anatomy of nephritis saturnina and early renal lesions in lead poisoning may be classified in *two main ways*: 1. According to the opinions concerning the part of kidney in which pathological anatomical changes begin first. II. According to the opinions as to the type of nephritis produced by lead poisoning. According to the classification of either one of these two ways there are three distinct groups of authors.

I.—If we divide the authors according to the first consideration, we shall find one large group of authors, who state that primary damages are produced in the parenchymatous units, glomerular and tubular epithelium. The second large group thinks that the blood vessels and capillaries are primarily damaged. The third group, however, states that the changes are coordinaate and not subordinate to one another; that they are the effect of the same cause, acting simultaneously on different tissues.

II.—Classification according to the type of nephritis produced by lead poisoning shows three main opinions among authors. 1. The largest number of these believe there is first an acute parenchymatous glomerulo-tubular nephritis, followed by chronic interstitial nephritis with secondary contracted kidney (granular kidney). 2. Another group is of the opinion that the nephritis saturnina begins with atherosclerosis of the larger and smaller renal arteries and terminates as primary, or genuine contracted kidney. A few authors of this group mention acute nephritis saturnina with parenchymatous degeneration as very rare. 3. The third group combines the opinions of the two preceding ones.

Namely, like the first group, they too state that there is an acute parenchymatous glomerulo-tubular nephritis saturnina, followed by chronic interstitial nephritis with secondary contracted kidney, but in addition to that claim that there is a complication of the just mentioned picture by damage to the blood vessels, consisting of degeneration of muscle coat, thickening of vessel wall, hyaline degeneration, atherosclerosis or obliteration of lumen. 4. As a fourth group here may be mentioned that there are reported a few instances, where authors found only parenchymatous degeneration in the kidney without any interstitial changes.

Since those who found exclusive or predominant changes in the parenchymatous parts of the kidney with secondary contracted kidney state that the process begins with glomerulo-tubular degenerative changes, and others regard it as primary in the blood vessels, I shall analyze the literature according to the type of nephritis, noting in each group its opinion concerning the primary origin of the process.

Group I.—With the exception of Ophüls (34) 1907, and Stieglitz (40), who are of the opinion that the changes in kidneys are coordinate and not subordinate to each other, all other authors of this group think the process begins in the glomerulo-tubular epithelium.

Bright (4) noted a connection between plumbism and albuminuria, and contracted kidney, which was confirmed by *Tanquerel des Planches* (42). *Charcot* (6), and *Charcot et Gombault* (7) thought the tubular alterations primary and the interstitial and vascular lesions secondary to these. Albumin was noted only with hematuria. Besides the usual features microscopically they found lime salts in the thin portion of Henle's tubuli and proliferation of epithelium in the tubuli contorti. The final stage of this lesion they called "cirrhose epitheliale" *Maier* (27) thought the character of the damage in chronic lead poisoning was a parenchymatous degeneration with resulting connective tissue induration. *Lublinski* (23) found in the urine of two persons poisoned with lead: albumin, epithelial cells, blood cells, granular cylinders; and he supposed that contracted kidneys existed, but these were not examined. It will be seen from these statements that albuminuria in lead poisoning is reported as conspicuous only in advanced cases, also the finding of blood in the urine by Charcot et Gombault, and Lublinski.

Prévost et Binet (37) say that divers phases of the nephitis saturnina finally terminate in interstitial nephritis with sclerosis, diminution in size of the kidney and very often cyst formation. They noticed yellowish, refractive incrustations, which they thought were lime phosphates. *Oliver* (31), besides parenchymatous degeneration also found fatty degeneration in acute parenchymatous nephritis, and states: "As these are, apparently, the early stages of acute lead poisoning, alike in man and animals, I regard them as characteristic of plumbism." Later he saw what he thought was true interstitial nephritis. *Stieglitz* (40)

reports experiments on rabbits and guinea pigs varying in time from 6 to 241 days. He found parenchymatous changes most often in the tubuli contorti and hyaline degeneration in the glomeruli. Hyaline cylinders were seen mostly in tubuli contorti; in some cases lime salt impregnations. He found also chronic interstitial nephritis with rich increase of nuclei around the tubuli and blood vessels. Arteriosclerosis alone in the kidneys or even in general arteriosclerosis is regarded as rare. He is also an advocate of the coordinate theory of the kidney lesion in lead poisoning. I especially call attention to Oliver's statement, that he regards the parenchymatous and fatty degenerations as the primary conditions occurring in the early stages of acute lead poisoning, because, as we shall see later, I found the same degenerations as the early lesion of acute lead poisoning.

Paviot (36) called attention to the frequent occurrence of a productive interstitial nephritis besides all the tubular alterations. *Jores* (19) expresses himself against the origin of the process in the blood vessels and denies any analogy between experimental and human lead nephritis. He saw lime salt deposits especially marked in the guinea pigs. Further he saw parenchymatous changes, lesions of the epithelium, albumin in capsular spaces, hyaline cylinders in dilated tubuli and blood pigment in tubuli (p. 205). Other than small patches, he saw connective tissue growth only in one animal, which lived the longest experimental time (p. 183). He thinks parenchymatous degeneration may be not the result of a direct action of lead, but perhaps of a general anemia caused by lead (p. 214). His denying of any analogy between experimental and human lead nephritis does not seem very convincing. It should not be forgotten that, while experimental lead nephritis is due only to the lead, this hardly can be said of human lead nephritis, where, besides the lead, practically always some other reason for the nephritis may be found; such as age, alcohol, syphilis, etc. The differences should be considered from the standpoint of the differences in etiology and the final stages of the process as seen in the human cases when examined. His finding of albumin in the capsular space is quite important, because the other authors, so far as I know, do not report such a finding; and because, in a positive case, there arises the question as to the source of this albumin, whether from the blood plasma filtrated through the glomerular wall, or from the degenerating glomerulo-capsular epithelium. To my mind it must be from both sources, because without alteration in the filter epithelium such a quantity of albumin from the blood plasma would not be present in the capsular space; and when this epithelium is degenerated it not only produces waste albumin, but, of course, allows more albumin from the blood plasma to pass, as is pointed out by *Cushny, A. R.* (p. 202) (10). I might add that in some of my cases there was precipitated albumin in the capsular space. Regarding the indirect cause of the degenerations, there are contrary opinions, as for example Legge and Goadby, who think that the

primary lesions are due to direct action of lead poison.

Kobert, R. (21) speaking about Phosphor, Plumbum and Alcohol poisoning says: "Die Nieren sind bei akuten Vergiftungen meist geschwellt, während sie bei chronischen cirrhottisch verkleinert sein können. Auch Verfettung, Embolisierung und multiple Blutaustritte sind nicht selten." In experimental animals he did not find any distinct cirrhosis of the kidney; interstitial or parenchymatous inflammation is seen.—In my opinion this may have been due to insufficient length of time for definite cirrhosis to develop.—He says that no metallic poison has so characteristic an effect on the kidney as lead. The excretion of even small quantities exerts an injurious action on the cells of the parenchyma, destroys them and eventually sets up a true cirrhosis.

Ophüls, W. (34) experimented with guinea pigs and dogs. Those animals which lived for a comparatively shorter time, about 2-6 months, showed only parenchymatous degeneration, necrosis and desquamation of epithelium of tubuli contorti and ascending part of Henle's loop. Usually he found regenerative evidence in this epithelium. In some cases pigmented epithelium, and occasionally slight fibrosis of the glomeruli and slight thickening of the glomerular capsule were found. Sometimes he found casts, but they were not very numerous. In animals which lived 1-3 years, he found "marked chronic interstitial nephritis," actual granular kidneys with narrow cortex, collapse of tubuli over large areas, marked intertubular fibrosis and casts. In the urine of dogs he was not able to find either albumin or casts and writes: "This observation gives support to the clinical suspicion that in man also such lesions may develop with very little, if any, change in the urine." No calcareous infarcts were found in these kidneys, and no vascular lesions of the aorta or in branches of renal arteries. He states that this nephritis does not resemble human nephritis, but is comparable to experimental uranium nephritis. He is an advocate of the coordinate theory of commencement of the renal lesion and rejects the subordinate theory (1907). It will be noted that Ophüls did not find many casts in the kidneys of guinea pigs, and neither albumin nor casts in the urine of dogs; as will later be seen I also found but little albumin and few casts in the urine of my experimental animals. Further, since it seems an important fact, if true, attention is again called to his statement regarding the clinical suspicion that in man such lesions, without urine changes, also may occur.

Ryle (39) reports concerning the wife of a tinsmith who for a long time washed her husband's clothes. He found chronic interstitial nephritis, small contracted kidneys with granular surface. Microscopically very little remaining kidney substance was found. Urea content of the blood was 2.46 grams per 1000 ccm, or eight times the normal amount. He thinks the female is more susceptible to lead than the male. *Rathery et Michel* (38) report the instance of a woman who took small doses of lead subacetate for fifteen days. The authors

found the most important lesions in the tortuous and collecting tubuli. Besides parenchymatous degeneration, necrosis and desquamation of the epithelium of the tubuli contorti, collecti and ascending parts of Henle's loops, they found intraglomerular hemorrhages with some round cells, proliferation and hypertrophy of the cells of the Bowman's capsule, which were pear shaped or elongated, and certain of these cells were filled by fine granules. A large proportion of the straight tubules were packed with granules from the tubuli contorti and, being already damaged, became completely impermeable. In the interstitial tissue, around glomeruli and straight tubuli, there was found round cell infiltration. This case is in contrast to the opinions of MacCallum, Legge and Goadby, and other authors from the second group, who base their opinions upon the human cases, and say that acute lead poisoning is rare (MacCallum), and only after large doses (Delafield and Prudden, F. C. Wood). *Aub. Fairhall, Minot and Reznikoff* (2) are of the opinion that chronic nephritis, supposed to be caused by lead, presents the picture of the typical secondary contracted kidney. *Gwyn, B. N.* (15) says: "A slight degree of albuminuria with some casts is not uncommon in the early stages, especially if the dosage has been large. Albumin and casts are frequently present during an attack of colic. After prolonged poisoning progressive chronic renal changes may become the most important feature of the case." According to my knowledge the findings of the authors of this group, who found as early renal lesions parenchymatous degeneration and fatty degeneration infiltration with swollen kidneys, and as chronic lesion secondary contracted, or granular kidney, are very logical and most probable. It is also important for the prognosis of the kidney disease of such a nature that several authors noted the regeneration of the tubular epithelium.

Group II.—This group of authors is of the opinion that the nephritis saturnina starts with primary changes in the blood vessels and terminates as a primary, or genuine contracted kidney.

According to *von Leyden* (44) lead nephritis is identical with Virchow's atrophic granular kidney, or what he terms sclerotic atrophy, or what he In these the tubuli are diminished and partially tortuous, the interstitial connective tissue is increased and full of nuclei; the afferent and efferent vessels as well as glomerular loops show exquisite hyaline degeneration. The glomeruli are contracted, shiny and homogenous. The intima of the larger vessels is very hypertrophic. His patient always had albuminuria. He thinks that parenchymatous degeneration is rare. According to *Gayler* (12) arteritis of the smallest arteries, which commences in the muscular coat, followed by endarteritis and obliterative arteritis, is the preliminary damage in lead kidney. *Strümpel, A.* (41) says the kidney of plumbism is the "genuine contracted kidney," extremely slow and chronic, but with constantly progressive atrophy of renal parenchyma and its substitution by cicatricial tissue. *Gull and Sutton* (14) have de-

scribed arteriocapillary fibrosis with great hypertrophy of the intima of the larger vessels. *Legge and Goadby* (22) state that lead nephritis is not acute, but of chronic cirrhotic type, which requires a long time for development; in animals two years. In the earliest cases interstitial nephritis is present, later changes in the glomeruli and fibroid degeneration take place, but even in this early stage interstitial hemorrhages without hematuria are present; the venules rather than the arterioles appear to be first damaged, intima being first affected, resulting in extreme narrowing and blocking of the vessels. "Parenchymatous nephritis may be seen, probably resulting from the transudation taking place from the vessel walls." It is interesting to point out so many "interstitial hemorrhages" only, always without blood in glomeruli or tubuli, and, naturally, without hematuria. The absence of hematuria, taken in connection with their plates, is not very convincing regarding interstitial hemorrhages. Their illustrations look more like a simple congestion. *Castex, M. R.* (5), according to clinical symptoms, thinks that there developed chronic interstitial nephritis, granular kidneys, on a vascular (arteriosclerotic) basis. He found albumin, epithelium, leucocytes, erythrocytes, hyaline and granular casts, and increased urea present. *Mechaitz und Rosenberg* (26) are of the opinion that saturnismus plays an important role in the etiology of "malignant kidney sclerosis." *Mallory* (28) says: "Lead poisoning is often blamed for vascular (arteriosclerotic) nephritis. *Delafield and Prudden, F. C. Wood* (11) are of the opinion that acute lead poisoning is present only with large doses and that in such case there may be fatty degeneration of the renal epithelium. In chronic lead poisoning kidneys are arteriosclerotic. *MacCallum* (25) thinks that acute lead poisoning is rare, and that chronic poisoning produces diffuse nephritis of the arteriosclerotic type. *Newburgh* (29) says chronic lead poisoning produces primary contracted kidney. He is also an advocate of the coordinate theory of lesion of the kidney. *Hamilton* (16) writes: "According to most authorities the underlying pathology of chronic lead poisoning is a structural change in the blood vessels (p. 20). The proliferative endarteritis is probably reparative and compensatory to the damage done to the muscular coat" (p. 22). According to her, in the subacute form of renal plumbism, changes are mixed; not only a thickening of the vessels with occlusion of the lumen, but a marked degeneration of the convoluted tubuli. On page twenty-nine of her book she quote: 'Volland (54), Mohr (55), and Stachelin (56)," but in the papers of the three authors, quoted in her bibliography, there is not a single word about either kidneys or about lead poisoning.

The important fact of the literature brought out by this group of authors is that they all state that albuminuria and vascular lesions are characteristic for lead kidneys, which, it appears to the writer, is due to the fact that they report, as well as the clinicians, their opinions concerning human cases, which obviously were chronic, for they showed distinct albuminuria and vascular lesions, which is not charac-

teristic for early lesions of lead kidneys. In such chronic human cases of lead poisoning, where albuminuria and vascular lesions were constant, they surely found hypertension and other symptoms of renal-cardiovascular changes, which, however, may not be due alone to the lead poisoning, but to the age of patients and to some other cause of renal-cardiovascular lesions, such as alcoholism, syphilis, and some other toxicosis or infection.

It is interesting that the authors of the second group, who are of the opinion that the primary renal lesions in lead poisoning are the vascular lesions, with the exception of Legge and Goadby, do not report experiments with lead poisoning, and Legge and Goadby, who do report experiments on cats, write: "Parenchymatous nephritis may be seen...." differing from the first and third group in that they place in the first rank, as most characteristic, "interstitial hemorrhages."

Group III.—In the third group have been placed those authors who believe the primary changes are of parenchymatous character, but that that there are also secondary vascular changes.

Here belong: *Cornil et Brault* (9), *Hoffa* (18); *Coen, E. e d'Ajutola, G.* (8) who, besides parenchymatous degeneration, necrosis and desquamation, describe glomeruli very rich in blood, proliferation of enthothelial cells and epithelium of tubuli contorti, hyaline degeneration of blood vessels and finally interstitial plastic nephritis. Hoffa studied rabbits and guinea pigs, while Coen and d'Ajutola studied rabbits. *Thompson* (43) is of the same opinion; both he and Coen and d'Ajutola often found albumin and different kinds of casts in the urine. *Oliver* (32) also mentions thickened arterioles as a frequent finding besides acute parenchymatous and chronic interstitial nephritis. *Page* (35) writes: "While it is difficult to deny the possibility of small amounts of lead a directly deleterious action on the musculature of the blood vessels, it would seem that the infliction of an injury on the renal epithelium is the first step in the process. The damaged cells then fail to excrete certain toxic substances from the blood, which being retained cause a rise in blood pressure and in time arteriosclerosis.—the damage is repeated, as also are the attempts at regeneration and repair, so that in time we have the sclerotic or granular contracted kidney." The human cases he reports showed albumin and casts present, also a rise in blood pressure. *Herrick, J. B.* (17) says that long continued action of lead may induce chronic nephritis, both parenchymatous and secondary interstitial, arteriosclerotic and amyloid kidney, and that in chronic intoxications one must assume the condition of the altered blood.

Group IV.—Few authors report that they found only parenchymatous or fatty degeneration, without any interstitial change in the kidney. *Anino* (1) studied kidneys of dogs, rabbits and guinea pigs, and, besides parenchymatous and fatty degeneration, found only vacuoles and granular atrophy of protoplasma and hyaline degeneration of nuclei. He did not observe any interstitial changes.—The

explanation of such cases may be either due to the fact that the experimental time was not long enough, or that insufficient amount of lead was used in the experiments.

To obtain a clearer picture concerning albuminuria saturnina the findings of the following authors are of value: *Oliver* (33) in his observation of temporary and permanent albuminuria is of the opinion that albuminuria saturnina is not only functional, but is caused by a lesion of the kidneys. However he found albuminuria in only nine out of thirty-seven cases, that is, only twenty-five per cent. Besides such inconstant albuminuria, he noted anemia, pallor, edema and epileptiform attacks. *Giglioli* (13) says transient appearance of albumin, tube cases and, sometimes, of kidney cells may be the first sign calling attention to the lead poisoning. *Widal, F.* (45) states that plumbism causes Brightism, albuminuria, azotemia and high blood pressure, the consequence of which is encephalopathia. He is discussing human cases.—Finally *Lyon, G.* (24) subjected several rabbits for two or three months to subcutaneous injections of lead acetate, and, although the animals wasted and finally died, the effects on the kidneys were negative.

Further it appears to the writer sufficiently important to emphasize the opinions of Ophüls, Stieglitz and Newburgh that the injuries in the kidneys are coordinate and not subordinate, and that they are the effect of the same cause acting simultaneously on different tissues with varying vulnerability and different reaction time.

In general all the authors of the four groups agree that there are kidney lesions due to lead poisoning. The difference in opinion concerning the part of the kidney, in which the changes begin first, and the type of nephritis produced by lead poisoning, it appears to the writer, are due to the different stages of kidney lesions studied by the various groups of observers. Therefore, while the authors of the fourth group, who carried on their experiments for only a short period, could find no lesions or found only the beginning degenerations, cloudy swelling and fatty degenerative infiltration, the authors of the second group, who studied practically only human cases, dying with advanced lesions and perhaps further complicated with lesions of some other source as age, alcohol, etc., found mostly genuine contracted, or arteriosclerotic kidneys. That such is the case is shown by the fact that several authors of this group, such as: Von Leyden, Legge and Goadby, Delafield and Prudden—F. C. Wood, and MacCallum, speak also of parenchymatous degeneration and nephritis although they say "rare" or "may be seen." Review of the literature shows that the writers who state that parenchymatous lesions in the kidney are primary in lead poisoning base their observations upon experimental results in various kinds of animals, while those who believe the primary changes are vascular made no experimental studies, or at least fail to mention such.

According to Jores and Herrick changes in the lead kidneys are the result of anemia, while Legge and Goadby say the kidney suffers directly

from the effect of the circulating lead. The writer agrees with the belief of Jores and Herrick, but at the same time one must admit that the latter authors' idea may also be correct.

As the review of the literature shows fatty degenerative infiltration was the early lesion of the lead kidney, noted by: Oliver (31), Kobert, Anino, and Delafield and Prudden—F. C. Wood. It is not difficult to understand this, if one has in mind the nature of poison and marked anemia produced by it. The occurrence of proliferation and regeneration of the epithelial cells, as described by Coen, E., e d'Ajutola, Page, Ophüls W., and Charcot et Gombault, seems logical.

Blood was found in the lead kidneys by *Kleinenberger* (20), *Ockerblad* (30), Jores, Kobert, Coen, e d'Ajutola, Ophüls, and Legge and Goadby (the last two in the interstitial tissue).

It may be noted that *lime salt impregnations* in the kidneys of lead poisoning were seen by Jores, Prevost, et Binet, Charcot, Gombault, Paviot, Stieglitz, and *Beer, E.* (3).

Experimental

Brief Description of Clinical and Pathologic-Anatomical Findings

Since the clinical manifestations of all the animals were fairly uniform, a general description of these will suffice to cover this part of the work, and will avoid unnecessary repetition.

The first general symptom shown by the animals after four to five doses of 0.036 gram lead carbonate is increased sensitivity and excitability. Attacks of convulsions and symptoms of colic usually begin after a total of 0.2 to 0.4 gram of lead carbonate per os in five to six subsequent days has been given. Some animals will die in these convulsive attacks, others survive. Animals receiving a lesser amount of poison during this period of time, and surviving ones, begin to lose weight and to show anemia, poikilocytosis, anisocytosis, normoblasts and basophilic granules in red blood cells. Although Legge and Goadby (p. 78) state that basophilia is normal in the red blood cells of the guinea pig, my animals showed a distinct increase. The anemia and loss of weight are progressive if the animals are given constantly sufficient doses of lead carbonate to keep them sick, but insufficient to cause death. Later the animals become very emaciated and, when they are very ill, are quiet, depressed and feverish, take little or no food or water, fear noise or any kind of excitement. They die usually in conculsions with cramps in their extremities, opisthotonos or emprosthotonos. In the grave stages of the illness the animals are very weak, show delirium, weakness and paralysis first in hind legs.

The urine of those animals, dying early, e.g., after 0.5 gram of lead carbonate showed traces of slightly more than a trace of albumin, one to two leucocytes, several epithelial cells, and considerable triple phosphate crystals and amorphous salts. The urine of the animals dead after three to five grams of lead shows more albumin, but never a marked amount, the same kinds of cells, crystals and salts, as above mentioned; but never was blood

found in the urine. These are the general clinical findings varying only in degree in different animals according to the time and total amount of lead given.

In this connection it is important to note that in the later period of the experimental time the animals become within certain limits immunized against the lead carbonate, so that they continue to live even though two to four times the original dosage is given, depending, of course, on the period of the experimental time.

The cause of death of the animals is clear. They died usually in convulsions due to the lead poisoning and not from other disease processes.

Gross Appearance of Kidneys

With one exception the gross pathological picture presented by the kidneys was so uniformly similar that a single description will suffice for all. Grossly the kidneys showing fatty degenerative infiltration were increased in size, swollen, with smooth yellowish-white surfaces, in which distinct yellowish streaks and points were visible. Only one showed a finely granular surface, indicating secondary contracted kidneys. This kidney was that of the experimental animal, which lived longest (202 days) and received the largest amount of lead carbonate (7.28018 grams).

Microscopical Findings

The material is arranged according to the total amount of lead received.

1. Length of experiment 4 days, received 4 doses of 0.03306 gram each. Total 0.13224 gram.

Kidneys show extreme congestion, oedema and several casts. Epithelial cells of Henle's loops and distal convoluted tubuli are slightly vacuolated.

2. Length of experiment 5 days, received 5 doses of 0.03306 gram each. Total 0.1653 gram.

Kidneys show slight congestion, few casts and very few lime salt deposits in the proximal convoluted tubuli and Henle's loops. There is slight vacuolization of the epithelial cells of Henle's loops and distal convoluted tubuli. Small lesions of spontaneous nephritis in cortex.

3. Length of experiment 8 days, received 8 doses of 0.03306 gram each. Total 0.26448 gram.

The microscopical picture is the same as in No. 2, except for the small spontaneous lesion in the cortex.

4. Length of experiment 10 days, received 10 doses of 0.03306 gram each. Total 0.3306 gram.

Congestion; here and there in the lumen of the tubule precipitated albuminous network. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli are slightly finely vacuolated—probably due to fatty degenerative infiltration.—Slight parenchymatous degeneration.

5. Length of experiment 21 days, received 11 doses of 0.03637 gram each. Total 0.40007 gram.

Microscopically shows congestion, oedema; precipitated albuminous network and few casts in convoluted tubuli and Henle's loops. Some of the proximal convoluted tubuli show parenchymatous degeneration and absence of the nuclei. Epithelial cells of Henle's loops and collecting tubuli are slightly vacuolated. In the papillary part of the Henle's loops there are lime salt impregnations.

6. Length of experiment 21 days, received 11 doses of 0.03637 gram each. Total 0.40007 gram.

Microscopical examination shows congestion, edema; networks of albumin in proximal convoluted tubuli; small number of casts and depositions of lime salt in Henle's loops. Few lymphocytes in the pelvic mu-

cosa. Moderate cloudy swelling in proximal convoluted tubuli. Slight fatty degenerative infiltration.

7. Length of experiment, total amount, and microscopial picture is the same as in No. 6.

8. Length of experiment 13 days, received 13 doses of 0.03306 gram each. Total 0.42978 gram.

7 doses of 0.06309 gram each. Total 0.44163 gram.

Shows passive congestion, few hyaline casts in Henle's loops and and distal convoluted tubuli, some of casts being calcified. One larger calcified body in glomerulus—like space in the cortex. Slight fatty degenerative infiltration.

10. Length of experiment 14 days, received 14 doses (13 of 0.03306, and 1 of

FIG. 1.—From Guinea-pig No. 12. Hyaline casts and lime-salts in thin portions of Henle's loops in papilla.

Microscopically shows congestion, edema, precipitated albuminous network and few casts in the proximal convoluted tubuli and Henle's loops; in these there are few lime salt deposits. Epithelial cells of Henle's loops, distal convoluted and collecting tubuli are slightly vacuolated. Slight parenchymatous degeneration and fatty degenerative infiltration. Few lymphocytes in the pelvic mucosa, indicating slight pyelitis.

9. Length of experiment 15 days, received 0.03637 gram each). Total 0.46615 gram.

Microscopical picture is the same as in No. 9, except for more precipitated albumin and slight pyelitis.

11. Length of experiment, total amount, and microscopical picture is the same as in No. 10, except for the slight pyelitis.

12. Length of experiment 17 days, received 15 doses (13 of 0.03306, and 2 of 0.03637 each). Total 0.56864 gram.

Microscopically shows congestion, little albuminous precipitate, few casts and lime salt deposits, slight cloudy swelling and fatty degenerative infiltration.

13. Length of experiment 8 days, received 4 doses of 0.155 gram each. Total 0.62 gram.

Shows congestion, in some of the tubuli precipitated albumin and here and there a small cast, which in the papilla are impregnated by lime salt. Epithelial cells of the Henle's loops, distal convoluted and collectnig tubuli show fine vacuoles—fatty degenerative infiltration. Here and there one can find mitotic figures. Slight cloudy swelling.

14. Length of experiment 8 days, received 5 doses of 0.155 gram each. Total 0.775 gram.

Microscopically shows marked congestion, here and there precipitated albuminous network. Epithelial cells of Henle's loops, distal convoluted and collecting tubuli are finely vacuolated, indicating fatty degenerative infiltration.

15. Length of experiment 7 days, received 5 doses of 0.155 gram each. Total 0.775 gram.

Microscopical picture is the same as in No. 13.

16. Length of experiment, total amount and microscopical picture is the same as in No. 15.

17. Length of experiment 35 days, received 6 doses of 0.171 gram each. Total 1.026 grams.

Microscopically shows congestion and edema. In both convoluted tubuli and Henle's loops precipitated albuminous network occurs. In all segments of the tubule there are a few small hyaline casts, some of which, especially those in the papilla, are impregnated by lime salts. Some of the epithelial cells of the Henle's loops and distal convoluted tubuli are detached from the basilar membrane; some show plasmorrhexis, others are without nuclei, and most of them are slightly vacuolated. Slight cloudy swelling, and fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubuli.

18. Length of experiment 64 days, received 39 doses of 0.03637 grams each. Total 1.41843 grams.

Microscopically shows few casts and lime salt impregnations in papilla, vacuolated epithelial cells of the Henle's loops, distal convoluated and collecting tubuli—fatty degenerative infiltration—There are mitotic figures in epithelium of collecting tubuli.

19. Length of experiment 44 days, received 24 doses (14 of 0.06309, and 10 of 0.075945 gram each). Total 1.64271 grams.

Microscopically shows precipitated albuminous network in convoluted tubuli. A few hyaline casts, some of which are calcified, occur in distal convoluted tubuli and Henle's loops.

20. Length of experiment 54 days, received 27 doses of 0.075945 gram each. Total 2.050515 grams.

Exhibits congestion of glomeruli; precipitated albuminous network in proximal convoluted tubuli with slight parenchymatous degeneration of the epithelium; few hyaline and granular casts in the Henle's loops and distal convoluted tubuli. Lime salt deposits occur in four casts. Epithelium of Henle's loops, distal convoluted and collecting tubuli, especially papillary ducts, is finely vacuolated, indicating fatty degenerative infiltration. Here and there the nucleus of an epithelial cell stains very dark, and the protoplasma pinkish-blue, probably indicating proliferation.

21. Length of experiment 80 days, received 50 doses (39 of 0.03637) and 11 of 0.06309 gram each). Total 2.11242 grams.

Microscopically presents moderate congestion, and precipitated albuminous network in Bowman's capsule and proximal convoluted tubuli. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli are finely vacuolated, indicating fatty degenerative infiltration.

22. Length of experiment 80 days, received 50 doses (39 of 0.03637, and 11 of 0.06309 gram each). Total 2.11242 grams.

Presents networks of albumin in proximal convoluted tubuli. Epithelial cells of the Henle's loops and of the distal convoluted tubuli show distinct vacuoliation, while those

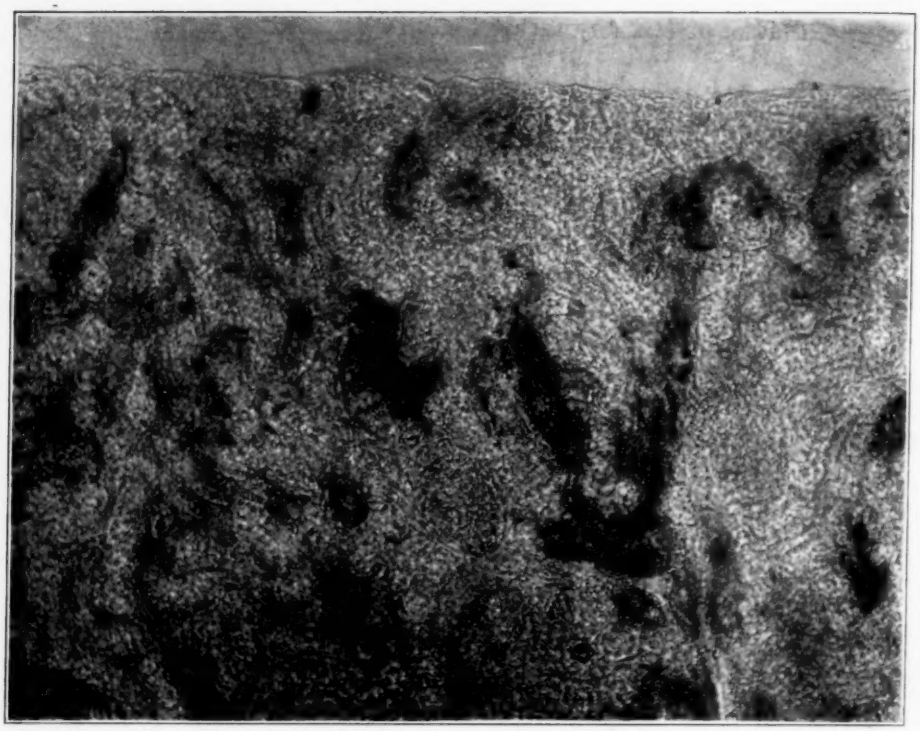

FIG. 2.—From Guinea-pig No. 20. Fatty degenerative infiltration of tubules in cortex. Scharlach-R stain.

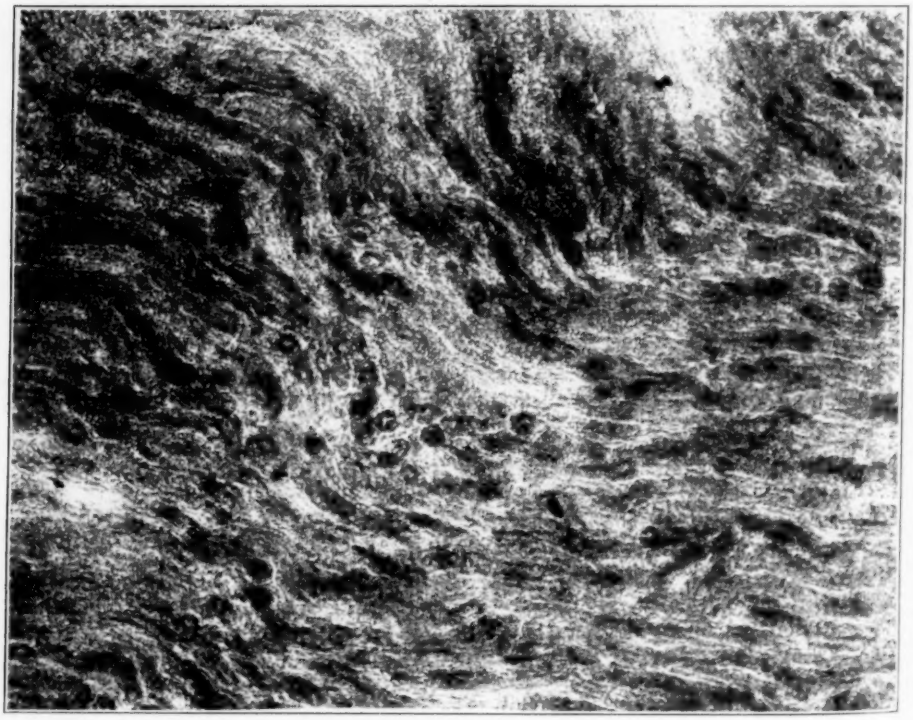

FIG. 3.—From same kidney as in Fig. 2. Scharlach-R stain. Fatty degenerative infiltration of epithelium of Henle's loops in cortical arch portion.

of the collecting tubuli are finely vacuolated —fatty degenerative infiltration.—Here and there are hyperchromatic nuclei and mitotic figures.

23. Length of experiment 85 days, received 51 doses (39 of 0.03637, and 12 of 0.06309 gram each). Total 2.17551 grams.

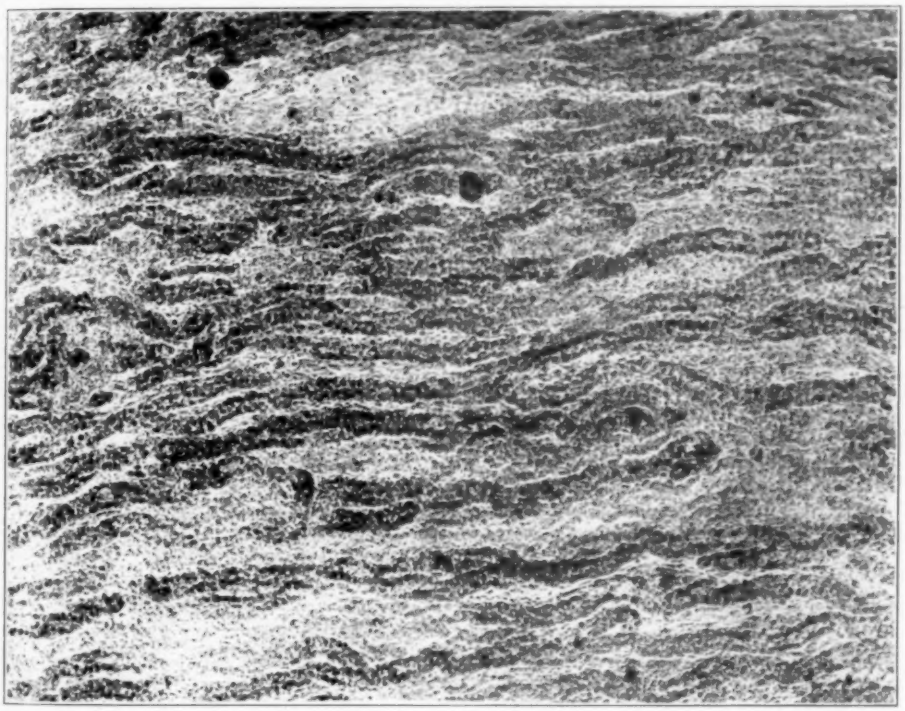

FIG. 4.—Medullary pyramid of same case. Scharlach-R stain. Fatty degenerative infiltration of tubular epithelium.

Presents precipitated albuminous network in the proximal convoluted tubuli, and few casts in the Henle's loops, most of which are infiltrated by lime salts. Fatty degenerative infiltration is indicated by the finely vacuolated appearance of the epithelial cells of the Henle's loops, distal convoluted and collecting tubuli. Occasionally hyperchromatic nuclei and mitotic figures are noted.

24. Length of experiment 54 days, received 16 doses of 0.171 gram each. Total 2.736 grams.

Microscopic picture presents marked congestion. In all segments of the tubules one can see precipitated albuminus networks and a few casts. Epithelial cells of the tubules are finely granular, and those cells of Henle's loops and collecting tubules are slightly vacuolated. Fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubules present. In addition there is slight parenchymatous degeneration.

25. Length of experiment 81 days, received 36 doses (6 of 0.06309, 19 of 0.075945, and 11 of 0.0909 gram each). Total 2.82148 grams.

Microscopically shows moderate cloudy swelling of the proximal convoluted tubuli, few finely granular and hyaline casts in the convoluted and collecting tubuli, and Henle's loops, in some of which lime salt is deposited. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli

are finely vacuolated, indicating fatty degenerative infiltration, which is less marked in the thin part of the Henle's loops and smaller collecting tubuli, than in the ascending part of Henle's loops, distal convoluted tubuli and papillary ducts, where it is very marked. Mitotic figures are numerous, especially in proximal convoluted tubuli, evidencing regeneration of the epithround, but some of them, especially in collecting tubuli, are flattened out and pushed rather toward the lumen, the cytoplasm being clear, swollen. Fatty degenerative infiltration is shown in Henle's loops, distal convoluted and collecting tubuli. A few hyperchromatic nuclei and mitotic figures are also present.

27. Length of experiment 81 days, re-

FIG. 5.—Guinea-pig No. 25. Osmic-acid preparation. Fatty degenerative infiltration of epithelium of collecting tubules near papilla.

elial cells. Slight connective tissue proliferation in the cortex is noted.

26. Length of experiment 59 days, received 19 doses of 0.171 gram each. Total 3.249 grams.

Exhibits congestion; in Henle's loops and collecting tubuli are a few hyaline casts. In Henle's loops, distal convoluted and collecting tubules the epithelial cells are very clear, vacuolated or goblet-like. The nuclei of these cells usually appear normal,

ceived 21 doses of 0.171 gram each. Total 3.591 grams.

Shows congestion, edema and very few casts. In proximal and distal convoluted tubuli, and Bowman's capsules one sees precipitated albuminous networks. Cytoplasm of the Henle's loops, distal convoluted and collecting tubules is slightly vacuolated and finely granular. In all segments of the tubules, here and there, one observes the absence of nuclei; and also

hyperchromatic nuclei and mitotic figures. Nuclei of the distal convoluted tubules are situated rather toward the inner border of the cell. Cells of the collecting tubules are mostly detached from basilar membrane.

Diagnosis: Fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubules. Regeneration of the epithelial cells of all divisions of the tubules.

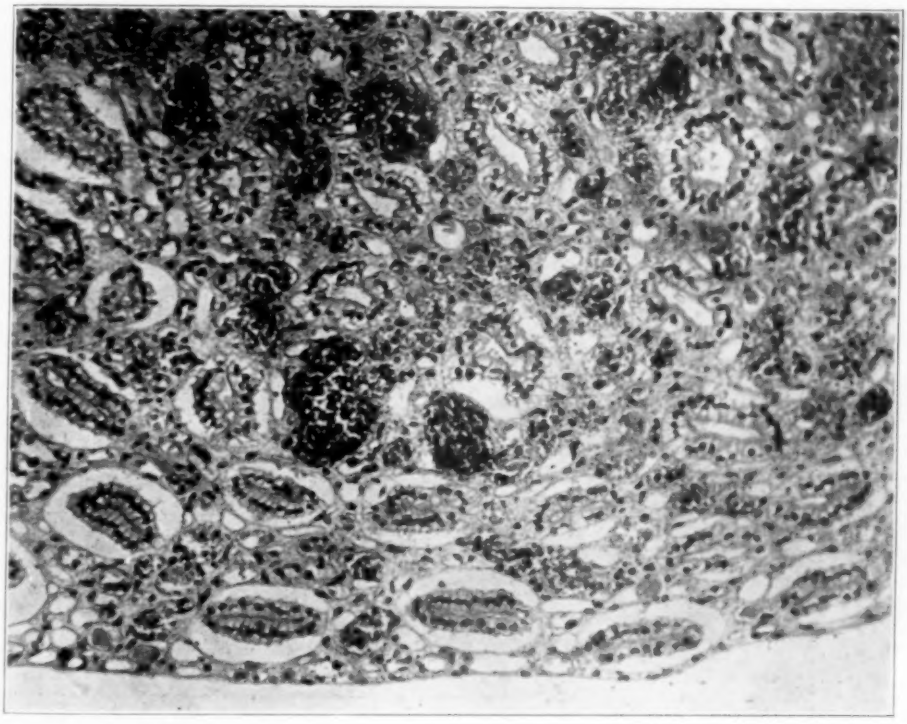

FIG. 6.—Guinea-pig No. 28. Hyaline casts and lime-salts in tubules of medullary pyramid, near papilla.

28. Length of experiment 57 days, received 22 doses of 0.171 gram each. Total 3.762 grams.

Shows little congestion, and in Henle's loops but few hyaline casts. In several of these casts (4 to 5) one can see small, dark-blue, rounded, structurless bodies, which correspond in their appearance to lime salt incrustations. In the papilla there are many such incrustated areas between the collecting tubules. Protoplasm of the cells of distal convoluted tubules and Henle's loops is clear and more granular than normal. The inner margin of these cells is irregular, and in the lumina of such tubules one can see albuminous precipitate, sometimes in a network. The smaller collecting tubules show the same thing. In the larger ones, however, cells are detached from the basilar membrane; and the lumen is narrow or lacking, because due to the fact that the inner margins of the cells are either very close or approximate each other. Some of the nuclei of these cells are somewhat flattened out and lie rather toward the basilar part of the cells. Cytoplasm of these cells is clearer than normal, especially around the nuclei and basal part of the cells. There is a fatty degenerative infiltration of Henle's loops, distal convo-

luted and collecting tubules. Lime salt deposits are present in Henle's loops, collecting tubuli and in straight medullary rays. Parenchymatous degeneration in proximal convoluted tubuli is noted.

29. Length of experiment 93 days, received 53 doses (20 of 0.06309, 24 of 0.075945, and 9 of 0.0909 gram each). Total 3.90266 grams.

Microscopically shows a moderate degree of cloudy swelling in proximal convoluted tubuli and precipitated albumin here. In Henle's loops, distal convoluted, collecting tubuli and papillary ducts the epithelial cells are finely and coarsely vacuolated indicating fatty degenerative infiltration. There are very few casts. In all portions of the tubule one can see single desquamated epithelial cells of the proximal convoluted tubule epithelial type. Mitotic figures and regenerated epithelium, especially in the proximal convoluted tubule, are readily demonstrable. In the fatty tissue of one or two of the interlobular septa there is slight polymorphonuclear infiltration.

30. Length of experiment 95 days, received 55 doses (20 of 0.06309, 24 of 0.075945, and 11 of 0.0909 gram each). Total 4.0844 grams.

Microscopically presents parenchymatous degeneration and precipitated albumin in convoluted tubuli, finely granular and hyaline casts mostly in the Henle's loops located in the papilla, few of these casts containing lime salt. In collecting tubuli and papillary ducts may be seen clumps or casts of desquamated epithelial cells. Fatty degenerative infiltration is quite marked in the usual parts of the tubule.

31. Length of experiment, total amount of lead and microscopical picture are the same as in No. 30.

32. Length of experiment 161 days, received 98 doses (12 of 0.03306, 41 of 0.03637, 38 of 0.06309, and 7 of 0.075945 gram each). Total 4.816825 grams.

Microscopically presents dilated Bowman's capsules and proximal convoluted tubules filled with precipitated albuminous network, and few casts in the Henle's loops. Epithelial cells of the Henle's loops, distal convoluted tubuli and in lesser degree collecting tubuli show fatty degenerative infiltration. Albuminous precipitate in capsular space would indicate also the lesion of the capsular epithelium. In the Henle's loops and collecting tubuli are several deposits of lime salt.

33. Length of experiment 180 days, received 109 doses (40 of 0.03637, 38 of 0.06309, 20 of 0.075945, and 11 of 0.0909 gram each). Total 6.37111 gram.

The pathological picture shows less fatty degenerative infiltration, but more hyaline casts than that of the No. 32, and several foci of small round cells. The important thing in this and the following three animals in the presence of small foci of very dark fibroblastic nuclei in the cortical zone, indicating beginning of secondary interstitial nephritis.

34. Length of experiment 180 days, received 113 doses (40 of 0.03637, 39 of 0.06309, 23 of 0.075945, and 11 of 0.0909 gram each). Total 6.662035 grams.

Pathological picture is similar to No. 33, but with more casts, lime salt in convoluted tubuli, and epithelial regeneration in the proximal convoluted tubuli. Very early connective tissue proliferation in the cortex.

35. Same as No. 34.

36. Length of experiment 202 days, received 130 doses (12 of 0.03306, 44 of 0.03637, 39 of 0.06309, 24 of 0.075945, and 11 of 0.909 gram each). Total 7.28018 grams.

Grossly shows uniformly finely granular surface.

Microscopically presents cloudy swelling of the epithelium of the proximal convoluted tubuli with precipitated albumin and few casts, which are present also in the Henle's loops. Fatty degenerative infiltration is not marked. Characteristic for this section is the presence of the cystic dilated tubules in the cortical zone; these cysts are lined by cubical or slightly flattened epithelium and contain hyaline casts or precipitated albumin. A futher characteristic feature is the proliferation of the interstitial connective tissue beginning at

FIG. 7.—Guinea-pig No. 32. Glomerular and tubular changes.

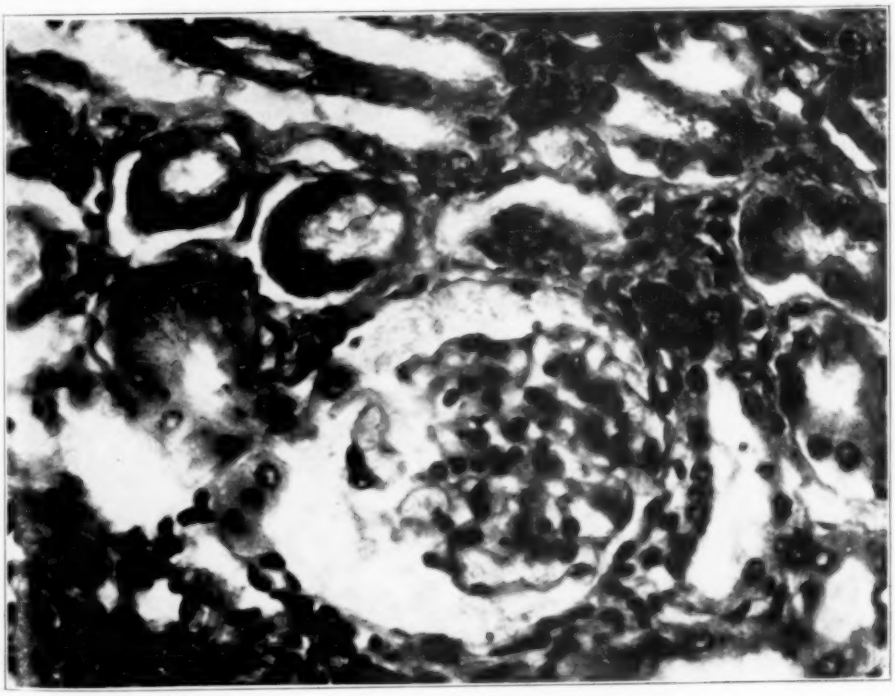

FIG. 8.—Guinea-pig No. 32. Higher power of glomerular and tubular lesions.

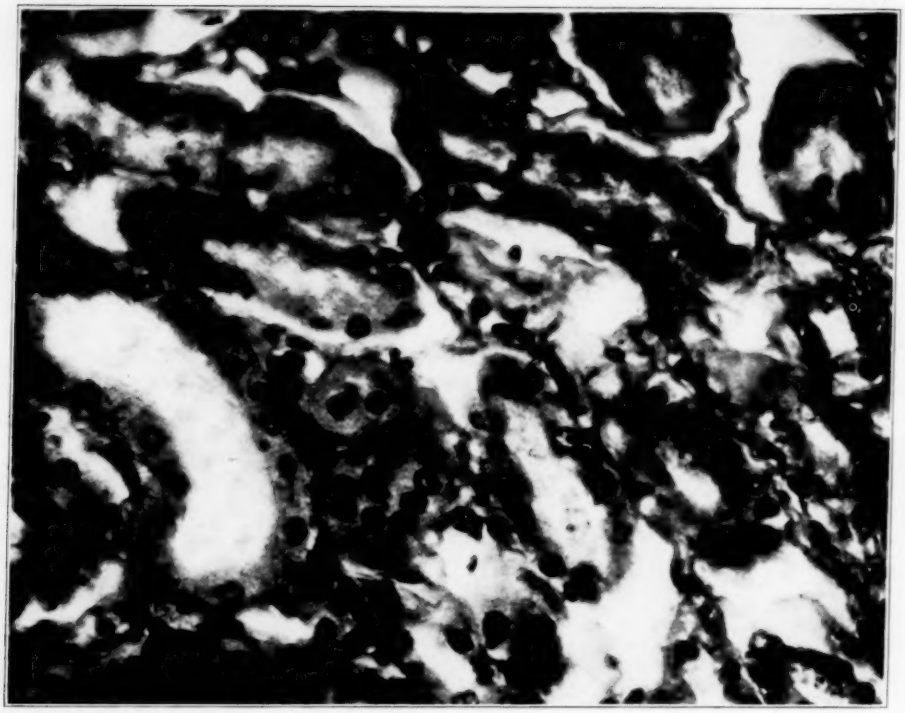

FIG. 9.—Guinea-pig No. 32. Tubular lesions.

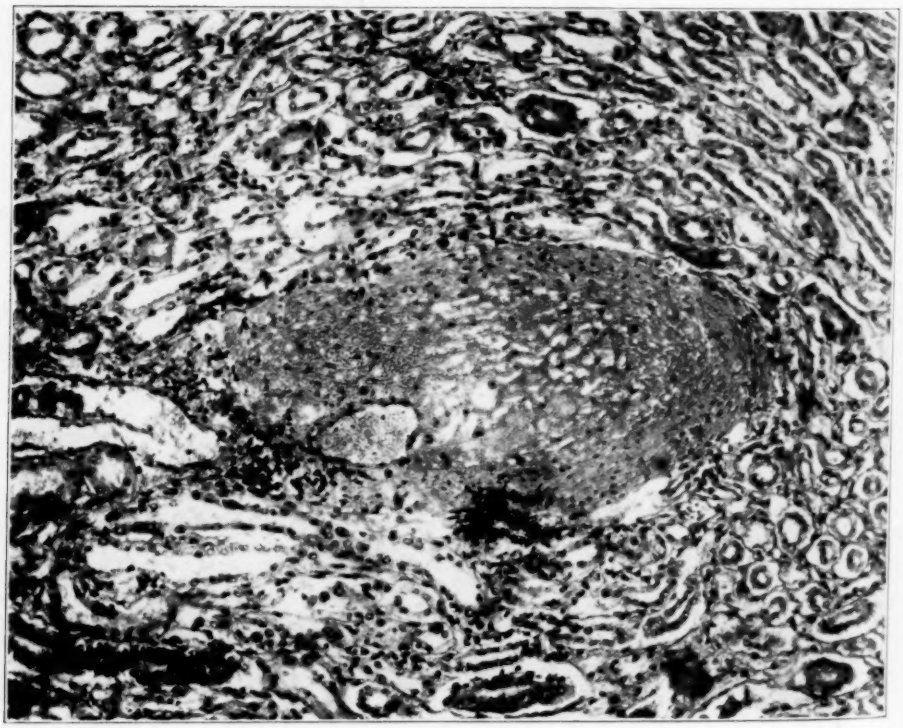

FIG. 10.—Small anemic infarct, with slight inflammatory reaction about it. Guinea pig No. 32.

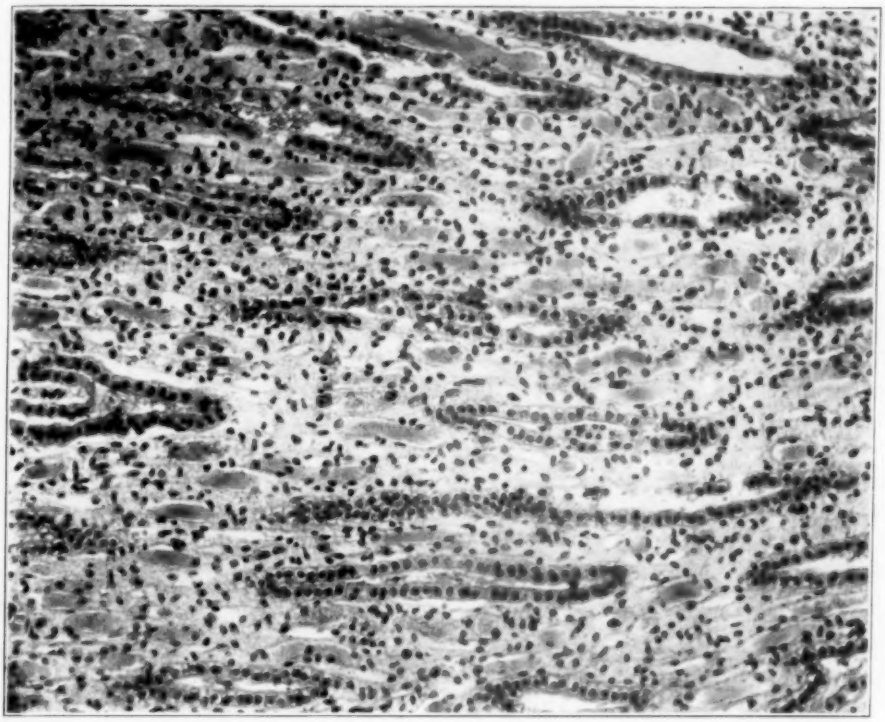

FIG. 11—Guinea-pig No. 33. Hyaline casts and hyaline thrombi in papilla.

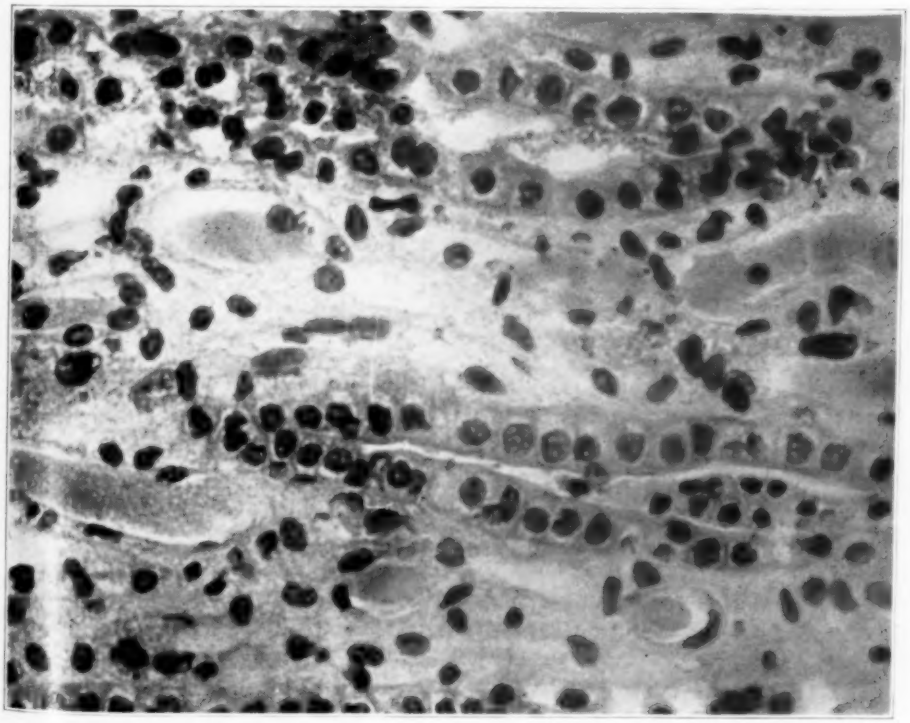

FIG. 12.—Higher power view of preceding.

the surface and extending deeper into the cortex.

General Discussion

It will be seen from the foregoing brief descriptions of the pathologic-histological findings in the kidneys of guinea pigs dying at varying experimental time and variable total dosages of lead, that the kidney lesions are mostly those of the initial stage, confined to epithelial damage, both in the renal tubules and Malpighian bodies. There are in the last four instances slight inflammatory changes in the kidneys, but in all others only those of circulatory and degenerative nature. The circulatory changes are expressed in the quite marked congestion, both active and passive, of the renal vessels and capillaries. This congestion is characteristic in most of these experimental animals with one or two exceptions. In agreement with Coen E. and e d'Ajutola, G. the glomeruli were usually found moderately or greatly congested. In several cases there was also edema and hydrops of the kidney structures. The most adequate explanation for this congestion seems to be the chemical irritation and altered metabolism of the kidney cells caused by poison, which irritation and change in metabolism causes a larger inflow of blood. An explanation on any other basis is difficult, because, according to Heubel (46), Rosenstein (47) and Siccardi (48), lead produces vasoconstriction and anaemia. Edema is simply the consequence of hyperemia, and hydrops in some cases is due to change in metabolism of the cells.

Although Legge and Goadby so strongly emphasize in their descriptions and illustrations interstitial hemorrhages in the kidneys of lead poisoning both in animals and in man, it does not seem convincing to us, since in our series we have frequently seen identical pictures in the lead kidneys, but these we find are only congestion, and not hemorrhage. They state that "the venules rather than the arterioles appear to be the preliminary site of destruction." From their descriptions and plates it would appear that they did not always find the delicate venule walls intact. This does not necessarily mean, however, that such defects are pathological; they may very readily have been artefact due to contraction or stretching of the sections during the technical preparation.

The next characteristic change is the slight parenchymatous degeneration of the tubular and glomerulo-capsular epithelium, particularly in that of the proximal convoluted tubules. In several cases in the capsular spaces and frequently in proximal convoluted tubules and even lower down there were present networks of precipitated albumin. However, in such early experiments albuminuria was not marked, corresponding to the findings of Oliver, Giglioli, and others, who in most of the cases found transient, or temporary albuminuria, and to the findings of constant albuminuria in human cases of chronic lead poisoning by Bright, Tanquerel des Planches, Lublinski, Von Leyden, Page, Castex, and Widal.

There were few hyaline and even a smaller number of granular casts, most numerous in the Henle's loops and collecting tubuli, but also occa-

sionally found in the convoluted tubuli. In several kidneys we have seen slight epithelial cell dequamation, and in three of these even epithelial casts could be seen in the collecting tubuli and papillary ducts. Proof that the thin parts of Henle's loops in the guinea pig kidney extend even into the papilla is offered by the finding of tubules in this location whose epithelial lining is that of this part of Henle's loop and, furthermore, by the presence of small and thin hyaline casts and lime salt deposits within the lumina of such tubules.

Attention is again called to the practically constant presence of lime salt deposits in the kidneys examined. As is generally known, the lime salt is deposited in areas of necrosis. Such is the case here also. These impregnations, it was found, begin primarily in the casts, and later, as they increase, lime spreads centrifugally into the adjoining epithelial cells and also the interstitial tissue. According to the distribution of the casts, the lime salt impregnations were most frequently found in the medullary pyramids in the papilla and near it, originating from the casts in Henle's loops and collecting tubuli and spreading toward the outside of the tubules. The lime salts were found in several instances in distal convoluted tubule casts also. In several instances, where the lime salts were in only small quantities, only a few granules, it was clearly demonstrable that the impregnation begins in the casts. This finding of lime salt deposits is in accordance with that of the authors mentioned in the discussion of the literature, particularly of Charcot, who found the lime salts in the thin parts of Henle's tubuli, and with those of Beer, E., who says: —"deposits in the connective tissues were extremely rare and adjacent to involved tubuli." Beer also noted the deposits in the papilla. In my preparations the lime salt was found to be calcium carbonate, since, upon application of sulphuric acid to sections containing the deposits, there developed gas boubles due to formation of carbonic acid gas (CO_2). The lime salt deposits found were better brought out in the Best's carmin preparations than in the hematoxylin-eosin sections.

The fourth characteristic of the early lesions of the renal tissue due to lead poisoning is fatty degenerative infiltration. This degeneration was not found in all the segments of the glomerulo-tubular epithelium. It is best developed in the epithelium of the ascending part of the Henle's loops, distal convoluted tubules and in the papillary ducts, and only in lesser degree in the collecting tubuli and thin parts of the Henle's loops. In no instance did the epithelium of Bowman's capsule and proximal convoluted tubuli show this lesion. The fat droplets are situated mostly in the basal part of the cells. In the last four instances showing the beginning interstitial proliferation the fatty degenerative infiltration was very slight, which is important in regard to the beginning of the inflammatory process. In order to determine whether or not fatty degenerative infiltration occurs in normal guinea pig kidney, four healthy animals were killed and their kidneys examined for fat. To elimi-

nate possible error due to excessive adiposity, animals of different body weights (468 and 496 to 610 and 740 grams respectively) were chosen. The kidneys of these animals were fixed and stained in exactly the same manner as those of the lead animals. No fat was found in these controls. Therefore the statement of some authors that the kidneys of normal, healthy guinea pigs show fatty degenerative infiltration is unconfirmed. In my opinion the finding of fatty degenerative infiltration in the kidneys of supposedly normal experimental animals may be due to the fact that they are latently ill because of improper diet or hygienic care. This demonstration of fatty degenerative infiltration in the kidney tubuli confirms the reports of Oliver, Kobert, Delafield and Prudden—F. C. Wood, and Anino. Whether or not these early degenerative lesions are due to direct action of lead upon the renal epithelium or are the result of anemia produced by this poison is uncertain. It seems possible that the deleterious results may be due both to the direct action of lead and to the anemia caused by it. However, the negative finding of fatty degenerative infiltration in the kidneys of animals, dying shortly after beginning of the experiments, would indicate that the fatty degenerative infiltration probably is not due to the direct action of the lead, at least not in those in which only a small amount is ingested, but rather to the anemia produced by lead, and thus to indirect action of the lead.

All these findings: circulatory changes, degenerative parenchymatous and fatty lesions, hyaline and granular casts and lime deposits are proof, that the earliest renal lesions, due to lead carbonate poisoning, are of a degenerative nature.

While all these lesions are of retrogressive character, there are instances of proliferative and regenerative nature also; since in several of kidneys examined very hyperchromatic nuclei, and frequently distinct mitotic figures of the epithelial cells were seen. These show rather bluish-pink protoplasm, oval shaped cells with the long axis usually in the circular or longitudinal direction of tubule, not, as normally, in the radial direction. This indicates regeneration of the damaged epithelium of the tubules. This finding confirms the similar reports of Charcot et Gombault, Ophüls, Coen E., e d'Ajutola, and Page.

Glycogen infiltration of the kidneys was not present in any of the experimental animals.

Likewise, there were no microscopic vascular lesions such as degeneration of the media or proliferation of intima in the kidneys of any of my animals, which is in disagreement with the opinion of the second group of authors, who believe that the vascular lesions are primary in the lead kidney. According to this negative finding of vascular lesions for the first six to seven months of the experimental time, during which epithelial lesions are demonstrable, the primary renal lesion due to lead poisoning is parenchymatous degeneration and fatty degenerative infiltration of the epithelium, followed by secondary

interstitial nephritis. If there are vascular lesions due to lead poisoning alone, as the students of human material report, these are only secondary and in very advanced stages of the lead kidney.

The beginning of secondary interstitial nephritis was found only in the last four animals i. e. in those which lived longest (6 to 7 months) and which had the largest amount of lead carbonate (6.37 to 7.28 grams). This was not very marked, but only in the first stage of interstitial proliferation with young dark nucleated fibroblasts, rich in cells, and without old scars or connective tissue hyalinization. This was marked only in the oldest animal in the outer zone of the cortical substance.

Although the number of animals living more than six months is too small from which to draw definite conclusions regarding the changes characteristic of chronic lead nephritis, so far as my results go they support the findings of Ophüls, who states that the character of the kidney lesions in experimental animals given lead carbonate less than six months is parenchymatous degeneration, necrosis, desquamation, and now and then regenerative evidence, characterized clinically by few casts and very slight or no albuminuria, and that the interstitial nephritis begins to develop secondarily, and only in those animals, which are experimented upon six months or more.

If we judge by the pathological lesions caused by different total doses of lead and various experimental time in several guinea pigs, we are forced to the conclusion that the changes in the lead kidneys are not dependent exclusively on the total amount of lead and experimental period. As we saw from the descriptions, the lesions and the degree of lesions are not absolutely the same in all of the animals, which received the same amount of lead for the same period; and on the other hand, there are similar lesions of the same or nearly the same degree in the animals, which received different amounts of poison for various experimental periods. Therefore, it must be noted that the kidney lesions in lead poisoning depend also upon an individual susceptibility, predisposition or resistance to the lead. This may be an inherited predisposition, susceptibility or resistance or it may be required in many ways.

Conclusion

On the basis of the foregoing results and from the discussion the following conclusions may be drawn:

1. That the earliest lesions in the guinea pig kidney due to lead carbonate poisoning are moderate parenchymatous degeneration and fatty degenerative infiltration of the renal epithelium, without any microscopial lesions of the blood vessels.

2. That these early renal epithelial lesions with resulting precipitated albumin, slight desquamation, moderate numbers of casts and lime salt deposits, providing that no other etiological factor can be found, are the only lesions up to six months duration of the experiments and when lead carbonate in amounts between 0.5 and six grams has been given. Both the time and amount of lead required to

bring on these changes is conditioned somewhat by individual variation in reaction of the experimental animals.

3. That after six months and when more than six grams of lead carbonate has been given there begins, first in the cortex, a slight proliferation of the interstitial connective tissue, which toward the end of the seventh month and when the total amount of lead carbonate given is over seven grams, leads to secondary contracted kidney.

In conclusion the author wishes to express his gratitude and appreciation to Dr. Aldred Scott Warthin and Dr. Carl V. Weller, under whose direction and guidance the work was carried out.

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Hookworm Disease Causing the Blood Picture of Primary Hemolytic Anemia in an Infant

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IN speaking of anemia in infancy Cabot (1) says there is apt to be (a) enlargement of the spleen, (b) leukocytosis, (c) high color index, with megalocytic blood picture, (d) erythroblasts, many of them megaloblasts, (e) abnormal leucocytes (myelocytes, stimulation forms), and that these findings make it so difficult in infancy to recognize the type of blood disease from the blood alone that the attempt should not be made—a view borne out in detail by the following case.

Case history: In October 1924, a twelve months old baby was referred to me by Dr. A. F. Thompson of Troy, N. C. The baby was very pale and weak, and had been vomiting about once a day for several months. The parents and other children seemed healthy. This baby was born at term and labor was normal. She had never been sick otherwise and was still almost exclusively breast fed. There was a history of having swallowed a small metal piece from a pocketbook at the age of five months, and at nine months the baby became yellow, pale and weak. The whites of the eyes were never yellow and the lemon-tint of the skin was not as pronounced as it had been at first. The child was very fretful and at times felt hot. The parents attributed the sickness to the foreign body.

On examination the anterior fontanelle was found to be the size of a dime; skin very pale with strong lemon-yellow tinge, sclerae white; throat, heart, and lungs negative. Three incisor teeth were present and one coming through. Peripheral glands were not palpable. The spleen extended an inch below the costal margin and the lower edge of the liver was palpable at the costal margin. An X-Ray examination by Dr. J. Rush Shull failed to reveal any foreign body. The child was found to be running a continued temperature from 100 to 102. The feces were strongly positive for occult blood and crowded with hookworm eggs. Examination of the blood showed hemoglobin 47%, red cells 2,470,000 giving a color index of approximately 1; leucocytes 12,000, with polynuclears 56%, small mononuclears 41%, large mononuclears 2%, neutrophilic myelocytes 1%, eosinophils 0. The red cells showed moderate variation in size and shape with some polychromatophilia. There were 360 normoblasts and 120 megaloblasts per cu. mm.

Because of the very poor condition of the child transfusion seemed advisable and Dr. A. G. Brenizer gave 120 cc of blood into the longitudinal sinus.

Hookworm disease is the last thing I should have suspected as the cause of anemia in an unweaned twelve months baby who not only could not walk but would not leave its mother's arms at all, for Darling (2) points out that "infants under one year rarely or never harbor hookworms."

The picture of primary hemolytic anemia (except for hemolytic icterus) is rare in childhood and extremely rare in infancy, but as Lucas (3) points out more than half the reported cases were supposed to be due to intestinal parasites. The anemia of hookworm disease is almost invariably of the chlorotic type with low color index but as pointed out by Dock and Bass (4) a few cases occur in which the number of red cells are reduced as much as the hemoglobin, giving rise to a color index of 1 or above.

During the summer the older children had taken the baby into the back yard and holding her up had tried to teach her to walk, selecting soft muddy ground to avoid hurting her feet.

As an intern in 1906, before much was known about hookworm in this country, I nearly killed a sixteen months old breast fed immigrant baby by starving it part of a day and giving thymol. The present patient, because of fever, anemia, and malnutrition, seemed too sick to stand much starving and purging. She was weaned and established on milk and oatmeal gruel before treatment was undertaken; then milk was withheld for a day before and after the giving of thymol, gr. 1, but during these two days oatmeal feedings were given at the regular intervals.

Dr. Thompson reports (1928) that after a number of treatments, covering a period of four months, all the hookworms were expelled, and the child has been normal ever since.

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Evidence Concerning the Effect of Insulin On Carbohydrate Tolerance

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PREVIOUS to the discovery of insulin the treatment of diabetes mellitus consisted entirely of dietary measures. Various writers outlined methods of procedure which were calculated to maintain a sugar free urine and still keep the patient fairly well nourished. These experiments met with a variable degree of success, depending on the severity of the disease in the patients under their care.

The discovery of insulin changed the treatment of this malady as no treatment has been changed before. The early writings on insulin which appeared shortly after the completion of the experimental work which led to its discovery, give one the impression that the remedy was destined only to control diabetes in all stages, (1). These experimenters were not willing to forecast an increase in the carbohydrate tolerance as a result of its use. This same conservative attitude is held by many writers today, (2).

As was true before 1922, diet is to-day the most important part of the treatment of diabetes. No case will progress favorably unless the diet is carefully adjusted to the patient's needs, and after the diet has been devised for a given patient that patient must be instructed in the proper preparation of the food and the calculation of the various amounts.

He should know why he is given a certain number of grains of carbohydrates, protein, and fat, and he should know how to properly calculate the amount of the various food substances. It has been my experience that the reliability of a patient, his ability to refrain from "cheating," depends to a great extent upon the character of the diet. If he can eat the same food that is served to others in the same family he will be better satisfied with his diet.

I have considered this matter in selecting a method of computing the diets given my patients. Dr. Orlando Petty (3) described such a method of diet calculation and it is his method that I have used. Patients using this diet are able to eat anything served in the average American home except pastry, pie, cake, candy, wheat bread, and other similar high starch foods. No extra cooking is required by the housewife in the diabetic family. This allows a more natural life and the tendency is towards honesty with himself and his physician.

The ratio between the protein, fat, and carbohydrate is so adjusted that there is no excess of anyone which

requires the addition to the diet of extra food materials such as olive oil, mayonnaise, cheese, cream in quantities greater than the usual person would enjoy. This is done by feeding the patient one gram of protein per kilogram of body weight, and sufficient fat and carbohydrate in ratio of 3 to 1 by weight, to make a total of 30 calories per kilogram. The ketogenic-antiketogenic ratio for diets calculated thusly is less than two and one quarter to one which leaves a safe margin, according to work done by Woodyatt (4).

Insulin has been used in cases placed on this diet, called by Petty an efficiency diet, when the carbohydrate tolerance of the individual was below the total glucose value of the diet. The patients are started on the diet and frequent blood sugar estimations are made. If the fasting blood sugar level falls to a level near normal, insulin is not used. If it fails to fall sufficiently or if it increases, insulin is used in sufficient amount to maintain the fasting blood sugar at a low level. This dosage is changed from time to time as the blood sugar permits. After the initial training period the cases are seen once a month for blood sugar estimations and the insulin dosage is adjusted accordingly. The insulin is divided into from one to four doses daily depending on the total amount to be given. It is injected just before mealtime, the fourth dose being given at midnight when necessary.

These patients are instructed to examine the urine weekly for sugar as an added precaution. However, I have discontinued relying on urinary sugar tests as a means of governing the dosage of insulin because I have found several cases where the renal threshold was so high or so low that the Benedict test was of little value. Several of these cases showed symptoms of diabetes, polyuria, polydipsia, and pruritus with a sugar free urine and after a more careful examination a high blood sugar.

William Brace (2) has recently shown that there is no improvement in the carbohydrate tolerance in cases treated by insulin and the Newburgh high fat diet (5). This is quite contrary to my experience and to work done by McCallum, J. R. Williams and others (6) (7) and (8).

I therefore wish to report several cases from my series as further evidence in favor of the opinion expressed by McCallum.

Report A—Case No. 14352. A woman, age 54, entered the hospital in April 1925 suffering from polyuria, polydipsia, burning on urination, pruritis and restlessness. She was obese and had lost no weight recently. The urine was positive for sugar and the blood showed a sugar concentration of 0.40%. She weighed 201 pounds and was five feet, one and one-half inches tall. She was placed on a diet of 1800 calories, and required fifty units of insulin daily to keep the urine sugar free and the blood concentration below 0.20%. After two weeks she was discharged on 35 units daily with a blood sugar of 0.18% and no symptoms. Two weeks later the blood sugar had reduced to 0.16%, accordingly the insulin was cut to 25 units.

She continued to improve and the insulin was gradually reduced until the following May when the blood sugar remained at 0.12% with no insulin. She has had no insulin since and the sugar concentration has been between 0.09% and 0.11% at six examinations over a period of 18 months.

CHART "1" REPORT A

Date	Blood sugar	Insulin	Date	Blood sugar	Insulin
4-2-25	0.400%	40 units	5-27-25	0.138%	25 units
3	0.182	40	6-12-25	0.133	24
4	0.250	50	7-14-25	0.143	20
5	0.222	50	8-14-25	0.099	16
6	0.222	55	1-14-26	0.101	8
7	0.200	50	2-14-26	0.115	4
8	0.200	50	4-16-26	0.200	6
9	0.200	50	5-18-26	0.091	0
11	0.182	50	7-1 - 26	0.093	0
12	0.182	50	9-16-26	0.100	0
13	0.154	40	1-3 - 27	0.237	0
14	0.182	40	6-13-27	0.092	0
15	0.182	25			

with the exception of one test which was 0.23% at a time when she was suffering from a severe bronchitis. Subsequent tests showed a return to normal, the last test being 0.09%.

Report B—Case No. 14180. This patient entered the hospital in March 1925, aged 41, complaining of polyuria, polydipsia, pruritus, and neuritis for the past 20 years. The urine was negative for sugar, acetone and diacetic acid, the blood sugar was 0.25%. She was placed on a diet of protein 60 grams, fat 100 grams, and carbohydrates 50 grams, and after two weeks the blood sugar level was constant between 0.18% and 0.19% on 37 units of insulin daily. All symptoms had disappeared and the urine remained sugar free. The diet was increased gradually from 1340 to 1600 calories, and has been kept at that figure ever since. She remained the same until September, 1925, when the blood sugar increased to 0.31% due to a nasal infection. After this infection subsided it returned to its previous level. In April, 1926, the sugar content fell to 0.13% and the insulin was gradually stopped. Since ceasing the injections the blood level has been constant between 0.14% and 0.16%. She is symptom free and has remained on the same diet continuously, with no change in body weight.

Report C—Case No. 13871. Five years previous to admission this patient was examined for insurance and was told he had diabetes. Three months later he was placed on a diet by his family physician. He gradually grew worse until one year before admission he was sent to a State institution for diabetic treatment. He was sent home on a high fat diet of 2500 calories and 84 units of insulin daily. On admission, in September 1924, he complained of pains in feet made worse by walking and worse at night; weakness, some nausea after eating and palpitation. Weight 155½, height 5'11½", age 37. The urine contained acetone and diacetic acid, but no sugar. The blood sugar was 0.408%. The diet was reduced to 1980 calories, consisting of 70 grams protein, 160 grams fat, and 65 grams carbohydrate. Gradually the fasting blood sugar lowered and the urinary ketone bodies disappeared. Sixteen days after admission he was ready to work, and complained of no pain in his legs. The insulin dosage during this time varied from 75 to 80 units daily. In January, he was returned to the hospital because the sugar content of the blood had again increased to 0.333%. This was shown to be due to a rise of blood sugar during the night as he had been having a series of attacks of insulin shock during the day. After a week, the blood sugar content was constant at 0.112% on 77 units daily. He remained on this dosage until August, 1926, when he was reduced to 67 units resulting in a blood sugar level during the next six months below 0.167%.

In May, he again returned complaining of frequent attacks of insulin shock and after several days in the hospital was readjusted on 32 units of insulin daily with a blood sugar level below 0.10%. He has remained sugar free and free from insulin shock from then to the present time, on 32 units daily.

Report D.—Case No. 18055. A woman, aged 52, was admitted in September, 1926, to the surgical wards following an automobile accident in which she suffered a torn buttocks and perineum. After four days she became unconscious and cyanotic and on examination the urine was found to contain a large quantity of sugar, acetone and diacetic acid. The blood showed a sugar contration of 0.4% and the alveolar air showed 15mm of CO_2 tension (Marriott). She was immediately placed on treatment for the impending coma. Fluids were administered subcutaneously. She was given digitalis tincture 15 minims every 3 hours and orange juice for its carbohydrate value.

She was given 150 units of insulin that day. That evening the sugar concentration had fallen to 0.18%. The following day she received 110 units of insulin and the alveolar CO_2 was 30. On the morning of the third day of treatment the sugar concentration had increased to 0.44%, but during the day by giving 205 units it fell to 0.80%. She had regained consciousness and appeared quite normal. However, she required from 85 to 100 units daily for several days before the alveolar CO_2 increased to 35mm tension.

On the sixth day she received her first food other than the large quantities of orange juice given her up to that time. She was placed on a diet of 948 calories and this was gradually increased to 1800 during the next week. The alveolar CO_2 gradually increased to 45 in 11 days and the insulin treatment fell to none in 33 days (see chart).

The healing of the perineum was hindered by considerable infection but was complete in about two months and she was discharged from the hospital in 67 days on no insulin and 1800 calories, with a normal

CHART "2" REPORT D

Date	Blood Sugar	Insulin	Alveolar CO_2	Blood Urea	Urine Sugar	Urine Acetone
9-9-26	0.476%					
	0.334					
	0.182	150 units	15 mm	28 mg	pos	pos
10	0.334	110	30		pos	pos
11	0.444					
	0.400					
	0.080	205	30		pos	pos
12	0.286	80	30	44	pos	neg
13	0.308	100	30	40	pos	neg
14	0.250	85	35	20	pos	neg
15	0.200	70	30	26	pos	neg
16	0.143	60	30		pos	neg
18	0.160	60	40	12	neg	neg
20	0.133	50	45	12	neg	neg
24	0.129	35		11	neg	neg
29	0.105	20			neg	neg
10-1-26	0.133	15			neg	neg
12	0.052	0			neg	neg
11-15-26	0.141	0			neg	neg
1-29-27	0.100	0			neg	neg
4-5-27	0.084	0			neg	neg
8-13-27	0.095	0			neg	neg

blood concentration. Since discharge she has had three blood examinations running from 0.08% to 0.10% with no urinary sugar and no symptoms.

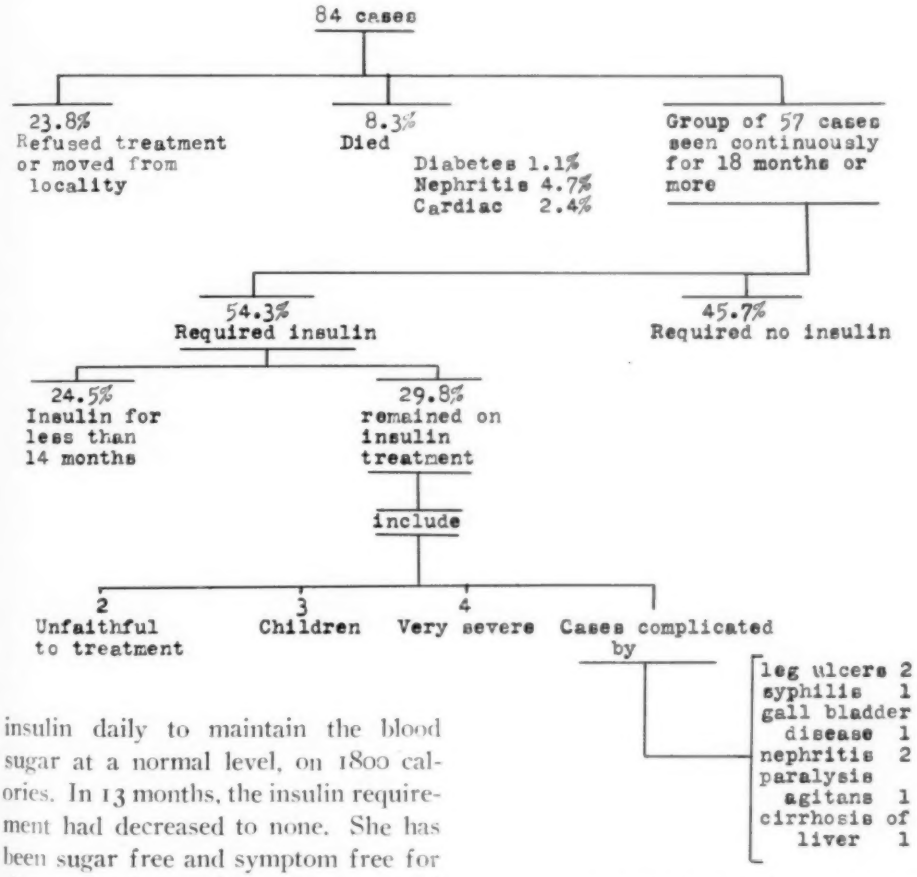
Discussion

Report A.—This presents the case of a woman who required 35 units of insulin daily to maintain the blood sugar at a normal level, on 1800 calories. In 13 months, the insulin requirement had decreased to none. She has been sugar free and symptom free for the past 18 months with a normal blood sugar and has remained on 1800 calories without loss of weight below the standard for her size and age.

Report B.—This case is very similar to the previous one. The patient was started at 37 units and continued to require this amount for 13 months after which it was gradually decreased and she has maintained a normal blood sugar level on no insulin for the past year and a half.

Report C.—This man was growing worse on 84 units of insulin daily and a 2500 calorie high fat diet. He did not believe his symptoms were due to diabetes because his urine had repeatedly been negative but on examination he was found to have a very high renal threshold, in the region of 0.40% blood sugar. When this was

CHART #3



reduced by readjustment of the daily spacing of doses his symptoms rapidly left him. He required between 75 and 80 units daily for 24 months. Following this his requirement has gradually reduced to 32 units. He has maintained a normal blood sugar level on this dosage for the past 8 months.

Report D.—This woman was first seen in diabetic coma. She required considerable insulin during the first week (800 units) in order to reduce the acidosis. After recovery from the ketonemia the insulin requirement rapidly fell to nothing. The infection which resulted in the wound probably accounted for the amount of insulin required, but as the infection subsided the requirement fell and she has maintained a normal sugar level on no insulin for the past year.

Of a series of 57 cases which have been observed for longer than one year, 45.7% required no insulin, leaving 54.3% which required insulin as well as diet, to bring the blood sugar to a normal level.

Of the 54.3% requiring insulin, 24.5% were able to cease the injections in from 2 weeks to 14 months, the average time being 5.9 months.

There remains a group of 29.8% who have continuously required insulin. This group consists of irregular cases, two of them have been unfaithful with their treatment both dietary and insulin, three of them are under 20 years of age and consequently more severe, eight cases are complicated by ulcers, syphilis, gall bladder disease, nephritis, paralysis agitans, and cirrhosis of the liver. There are four other complicated cases which belong to this group. One of these has been reported in this article. They all require less insulin than when first seen, but are classed as "very severe" with a very low carbohydrate tolerance.

Conclusion

This resume is offered as additional evidence that in the absence of complications adult diabetics gradually improve their tolerance for carbohydrate, many of them to the extent that insulin is no longer required.

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Addison's Disease in Association With Amyloidosis*

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AMYLOIDOSIS is infrequently associated with the cause of Addison's disease. Autopsy findings in a number of cases at the University Hospital show that amyloid deposit in the adrenal glands occurs in a fairly large percentage of those subjects showing a generalized amyloidosis. The amount, however, is quite variable and in only two cases is it present in sufficient quantity to suspect the causation of symptoms and signs referable to adrenal insufficiency. On account of indefinite clinical evidence, combined with the fact that the subject is a negro, one of these cases cannot be diagnosed Addison's disease, although the cortex of both adrenals is almost completely replaced by amyloid. The one case for discussion, however, gives definite evidence of Addison's disease in association with marked amyloidosis of the adrenals.

It is agreed that the primary etiology of Addison's disease is varied, and that tuberculosis of the adrenals is undoubtedly the most common pathologic finding in association with this disease. Neoplasm, gumma formation, atrophy, hypoplasia, hemorrhage, infarction, and roentgenray necrosis are also occasionally found in connection with this condition. Autopsy findings on patients dying in this hospital also show tuberculosis more frequently associated with Addison's disease than any other single condition. The review of 2550 autopsy cases reveals fourteen which can be classified under Addison's disease. The associated condition in these is:

Tuberculosis	7
Carcinoma metastases	4
Mycosis fungoides	1
Simple atrophy	1
Amyloidosis	1

Of these fourteen recorded, five are clinically diagnosed Addison's disease, and three others give a clinical diagnosis of (1) generalized tuberculosis with Addison's disease, (2) malignancy with Addison's disease, (3) chronic pulmonary tuberculosis with Addison's disease. The six remaining cases not clinically diagnosed give definite evidence of all six belonging to this group. On investigation, the clinical findings are found to be compatible with this diagnosis. Three additional cases give the typical pathological picture of Addison's disease, but there is no clinical evidence to substantiate the diagnosis.

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In regard to amyloidosis of the adrenals being a cause of Addison's disease, the literature shows only five other cases. All five showed marked amyloid deposits in the adrenals and have definite diagnostic proof of this disease being present. There are two additional reports by Riesman and Bauer which are somewhat doubtful; both show very marked amyloidosis of the adrenals, but neither gives a conclusive picture of adrenal insufficiency. Dickinson reports 118 cases of generalized amyloidosis, and of this number only nine show recognizable deposits in the adrenals; these cases show only a slight infiltration of the cortex with no apparent embarrassment to adrenal function.

A recent paper by Hunter discusses in detail the clinical and pathological findings in those cases previously reported. With reference to the adrenals, pathologic findings are fairly constant. The gross appearance shows the gland of normal or slightly increased size, increased firmness, yellow-white or grayish color, the cut surface giving a slight waxy appearance. Microscopic examination shows the amyloid in greater amounts in the cortex; the zona reticularis and fasciculata are most affected while the zona glomerulosa is only slightly involved. The medulla has only small deposits which are chiefly surrounding the blood vessels. All cases have a bilateral involvement of the adrenals.

Clinical Report

Mr. C. C., an American, carnival man, white, single, aged 45, entered the University Hospital November 2, 1927, complaining of weakness and pain in the abdomen. The symptoms had begun gradually six months before with a feeling of fatigue. He developed loss of appetite, nervousness, insomnia, and a continual dull headache. The patient lost 25 pounds in these six months. There were no gastro-intestinal upsets with vomiting. Gradual weakness with a beginning swelling of the feet and ankles forced him to seek medical attention.

Past History—He had pneumonia in childhood. He gives history of marked sexual excess and has had gonorrhoea four or five times, also syphilis, which was inadequately treated. Patient has been a steady though moderate drinker for many years. Was married for 17 years, had no children. Has been separated for past five years.

Family History—Father died at 80 of unknown cause. Mother died at 80 of a stroke. Two sisters died of tuberculosis, one sister of influenza, and another died at birth. Otherwise the history is negative.

Physical Examination—Shows a chronically sick man, who lies in bed with no marked discomfort.

Pupils: Small and irregular, reacting sluggishly to light and to accommodation.

Dental Hygiene: Poor, and caries, pyorrhoea and gingivitis are marked.

Tongue: Heavily coated with no pigmentation present.

Mucous Membranes: Pale and show no pigment.

Ribs: Very prominent showing evidence of loss of weight.

Respirations: 18 per minute.

Upper Lungs: Clear, but there is a flatness at both bases with distant breath sounds, and a few scattered, fine rales over these areas.

Percussion shows the heart enlarged both to the right and left.

Cardiac Apex: Felt indistinctly 12 cms. to the left of the mid-sternal line. The sounds are distant. No murmurs are present.

Pulse: Rate is 80 per minute, and feels weak and small.

Blood Pressure: 80 systolic, 50 diastolic.

Abdomen: Rounded and tense, with evidence of fluid in the flanks. The liver edge is felt easily, but the liver is not definitely enlarged.

Extremities: Pitting edema of both ankles. Knee jerks are not obtained.

Skin: Shows no evidence of pigmentation or discoloration.

X-ray Findings: There is a small amount of fluid in both pleural cavities, cardiac enlargement, pulmonary congestion.

Laboratory Findings: Urinalysis shows a trace of albumin, many granular casts, no red blood cells. P.S.P. Test: Shows 45% in two hours.

Non-protein Nitrogen: 32.7 mg. per 100 cc.

Peripheral Blood: Shows 80% (Sahli), 3,800,000 R.B.C., 4,200 W.B.C. The differential count is not important.

Blood Wassermann: Reacts 4 plus.

Course in Hospital: Was steadily downward. Developed a definite pericardial effusion, with a suggestion of pulsus paradoxus present. Edema became generalized. Temperature was always normal or subnormal up until two days before his death. Eleven days after his admission he developed a slight yellow discoloration of the skin over the lower face. This became more prominent, and deepened to a yellow-brown. At the time of death he showed a definite pigmentation of the lower face and upper neck. There also appeared to be increased pigmentation of both forearms. Blood pressure was 80/50 on three different occasions. The patient died fifteen days after admission.

PROTOCOL (abbreviated)

Mr. C. C., age 45. American, single, carnival man. Body is that of a white adult male of the typical asthenic type, with a light bony structure, and measures 161 cms. in length. Shows evidence of loss in weight in a fairly marked degree. Has long thin features. Neck is long and thin. Thorax is long and narrow. Intercostal angle is much less than a right angle. The intercostal spaces are depressed with the ribs prominent.

Skin is dry and inelastic. Over the greater portion of the body it is white, but there is a definitely pigmented area—yellow-brown in color—over the mid portion of the face. This begins on the bridge of the nose, and extends laterally and downward, over the lower face and upper portion of the neck. Both forearms and the dorsal surfaces of each hand show a definite yellow-brown pigmentation of the skin, which is contrasted with the white appearing and non-pigmented skin of the upper arms. Mucous membranes of mouth appear free of pigmentation grossly.

Left adrenal is slightly increased in size, and is surrounded by a moderate amount of fat. Cut section shows a strikingly hard and firm surface, which is wax-like in appearance. There is a definite patchy lipoidosis in the outer portion of the cortex.

Right Adrenal appears normal in size. Resembles the left in every other respect.

Microscopic Examination

Adrenals are almost completely replaced by amyloid, more marked in the medulla, and the inner portion of the cortex than at the periphery, where the glomerular zone and outer portion of the fasicular zone still show cells with excessive lipoidosis. Numerous syphilitic infiltrations are present in portions of the medulla. The large central vein is almost completely replaced by amyloid.

Semi-lunar Ganglia show marked deposits of amyloid in the ganglia and nerve trunks.

Pathological diagnosis is generalized amyloidosis of peculiar distribution, involving particularly the thyroid, pars intermedia of the hypophysis, heart and sympathetic nervous system, lungs, spleen, adrenals, pancreas, retroperitoneal vessels and the larger vessels of the hepatic trinity. Addison's disease. Old fibroid tuberculosis of lungs. Old syphilis. Syphilitic aortitis. Gumma of myocardium. Marked syphilitic pancreatitis, adrenalitis. Atrophy, chronic passive congestion and marked lipoidosis of all organs, particularly of the heart and kidneys. Myocardial failure. Hypertrophy and dilatation of both right and left ventricles. Relative tricuspid and pulmonary insufficiency. Thrombus of right auricular appendage. Hydropericardium. Hydrothorax. Ascites. Edema of the glottis. Asthenic constitution.

Comment

The clinical diagnosis does not include Addison's disease, but the symptoms and signs are quite typical of this condition. The findings of particular interest are: complaints of increasing weakness, steady loss of weight, persistent constipation, abdominal pain, and anorexia. He showed a definite pigmentation of the skin, hypotension, sub-normal temperature, a comparatively slow pulse, and a fairly marked anaemia. In a recent article by Rowntree, who has observed a large number of cases clinically, it is shown that the most frequent symptoms present are asthenia, pigmentation, loss of weight, constipation, vomiting, nausea, anorexia, and pain in the abdomen. Hypotension is present practically in every case, and is not infrequently accompanied by a sub-normal temperature, and anemia. Undoubtedly the three essential factors which should be present to make a definite diagnosis are: (1) asthenia, (2) pigmentation of the skin, (3) hypotention.

Pigmentation of the skin became apparent in this case only shortly before death. Records show a marked variation in the time of appearance. The report by Hunter states that pigmentation was first noted only three days before death. Rowntree observed that it appeared at varying stages of the disease, sometimes only present for a few days, in others for months, and in a few instances it was present for years. He also gives mention to the

variation in intensity of the pigmentation present, which may occur at different periods of the disease. Warthin reports a case of Addison's disease where pigmentation was definitely present over a period of more than four years.

Pathological findings in relation to the probable cause of this disease are very interesting. According to the views held by Wiesel the development of this disease is definitely dependent upon lesions of the chromaffin system, whether in the medulla of the adrenal or elsewhere in the body. Von Hansemann and Karakascheff disagree with this view and state cases of definite Addison's disease with only the cortex of the adrenals being involved, the medulla entirely escaping. Fahr and Reiche, and more recently McCutcheon also favor the association of Addison's disease to damaged cortex. McCutcheon holds that the rarity with which amyloid disease produces the Addison syndrome is not dependent on the preservation of the adrenal medulla, but rather on the fact that the cortex is not completely destroyed by the infiltration, many cell groups escaping. All five cases reported of Addison's disease caused by amyloid show a marked involvement of the inner two zones of the cortex with comparatively little damage to the medulla. This evidence definitely favors the presumption that damaged cortex and Addison's syndrome are directly connected. On account of the marked involvement of both cortex and medulla, the case now being reported does not favor either theory. It is proof, however, that amyloidosis of the adrenals, when present in sufficient quantity, will give the typical picture of Addison's disease.

In summary we have: (1) a case of Addison's disease with marked amyloid deposits in the adrenals, sympathetic semi-lunar ganglia, and nerve trunks, (2) amyloidosis is generalized, and associated with a combined tuberculous and syphilitic infection.

NOTE: Another case recently coming to autopsy warrants mention on account of amyloid deposits found in the adrenals with total absence of a similar deposit in any other organ of the body.

The clinical aspect given briefly is: A man of 59 entered the hospital complaining of weakness which had begun gradually five years before. The clinical picture and blood findings were compatible with the diagnosis of pernicious anemia. Satisfactory response was obtained by the administration of liver extract over a short period. Cardiac damage was very marked and shortly after admission he developed broncho-pneumonia which finally caused his death.

The findings at autopsy show the adrenals to be hypoplastic with a slight lipoidosis of the cortex. Otherwise the gross appearance denotes nothing abnormal. Microscopic examination reveals a marked atrophy in the medulla of both adrenals with many areas of amyloid deposit present. There is also moderately marked lipoidosis of the outer portion of the cortex.

The paramount points of the pathological diagnosis are: Primary adenocarcinoma of the prostate. Severe purulent prostatitis. Posterior urethritis and cystitis. Metastatic lobular purulent pneumonia with acute purulent broncho-pneumonia on an older organizing lobular pneumonia. Severe secondary non-hemolytic anemia. Atrophy of adrenals with amyloidosis.

The amyloid deposit in the adrenals shows moderately well with the usual hemotoxylin-eosin stain. This is shown definitely to be amyloid by the special Van Gieson stain. Though this subject manifests no evidence of adrenal insufficiency, it is of academic interest to note the occurrence of amyloid in both adrenals while those organs more prone to be affected have escaped.

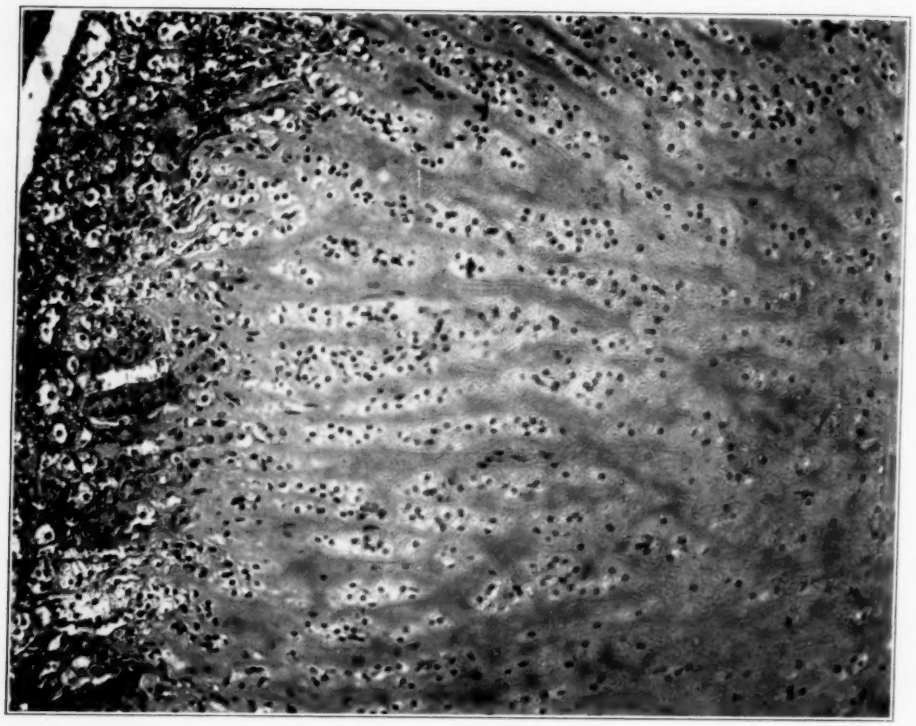

FIG. 1.—Extensive amyloidosis of adrenal, with Addison's syndrome. Generalized amyloidosis.

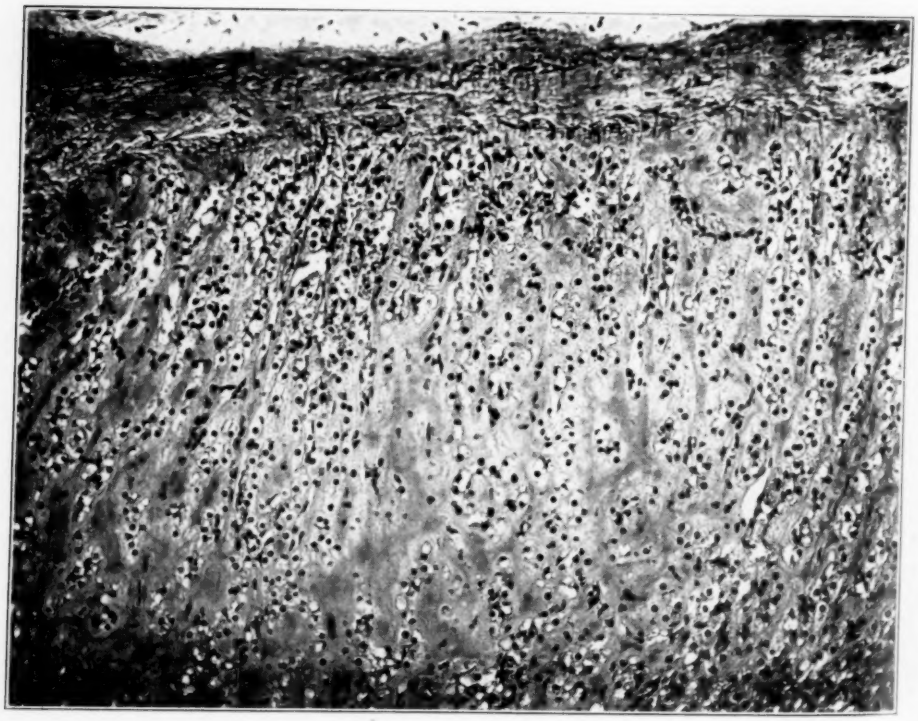

FIG. 2.—Other adrenal of same case. Both adrenals nearly wholly replaced by amyloid.

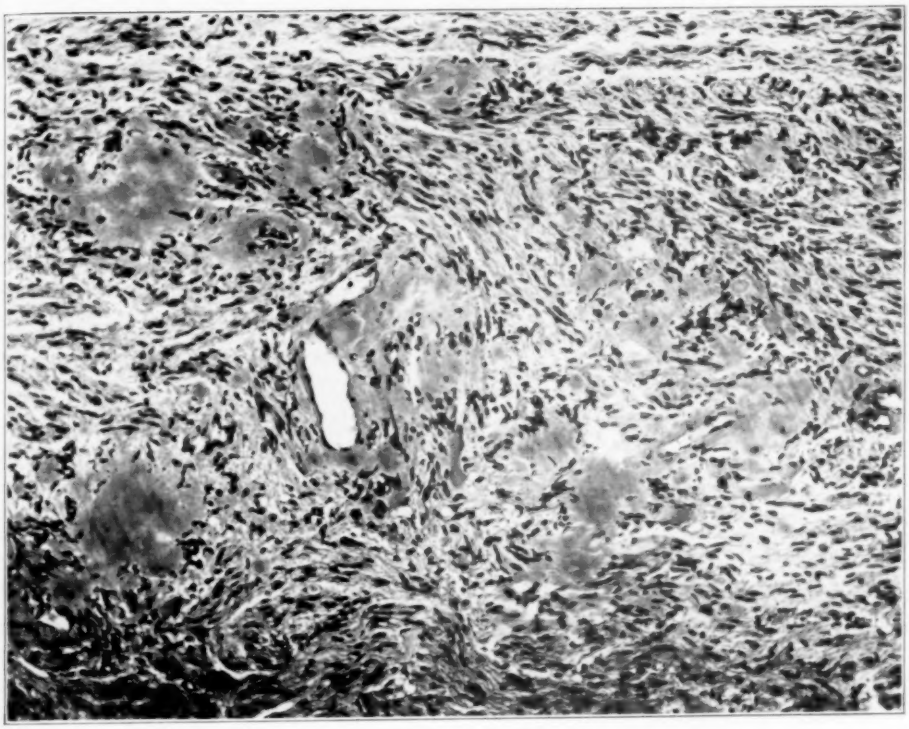

FIG. 3.—Amyloidosis of solar plexus. From same case as preceding.

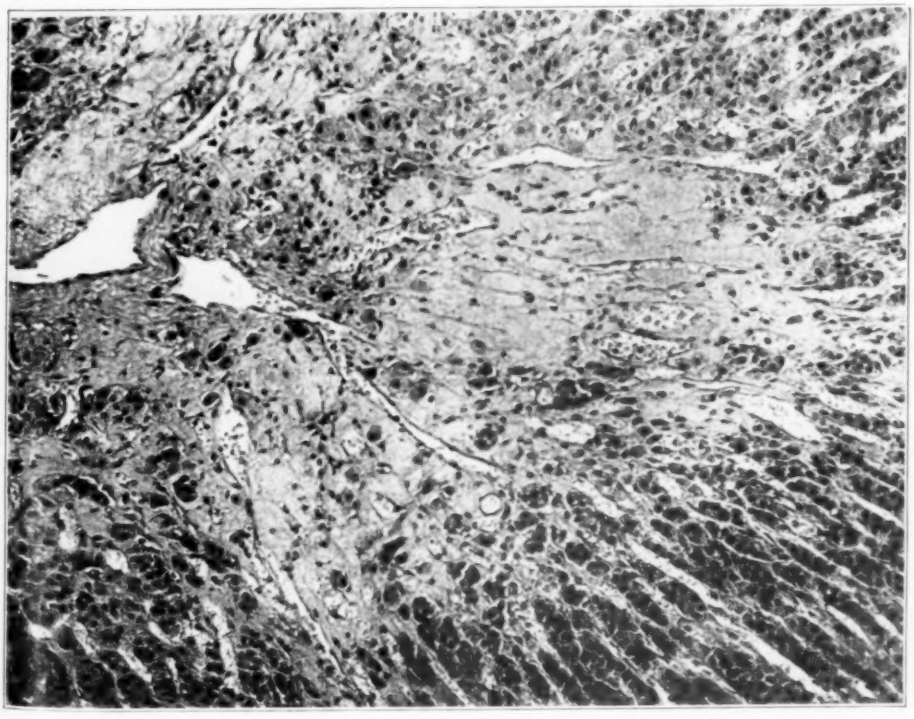

FIG. 4.—Area of amyloid in adrenal, around adrenal veins. Gave typical metachromatic staining reactions for amyloid. No amyloid found in other organ or tissue.

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Editorial

THE CONSTITUTIONAL FACTOR IN PEPTIC ULCER

The experimental attack upon the etiological problem of gastric ulcer has led to no conclusive results. Experimentally-produced ulcers, no matter by what form of local injury they have been developed, have all differed essentially from human ulcers in that they usually quickly heal, while in man gastric ulcer is characterized essentially by its markedly chronic course. Further, the effects of local trauma to the gastric mucosa vary greatly in different animals; no one of the causes adduced for ulcer production is constant in its action, and, so far as man is concerned, no etiological entity can be shown to exist in the form of extrinsic factors. We are confronted here by the same etiological problem as that of gastric cancer. Inasmuch as the general problem of cancer etiology has been cleared up by the animal experimental investigations of the last fifteen years which have conclusively demonstrated that intrinsic factors of constitution and organ-predisposition determine the origin and site of cancers, it is but natural that we should seek a similar explanation for ulcer of the stomach. If such intrinsic factors exist they must show themselves in heredity. It is necessary, therefore, in the first place to determine if there is any evidence of heredity in the case of gastric ulcer, and for this evidence we must turn to available statistics of gastric ulcer. Such evidence is singularly lacking in the textbook articles on gastric ulcer. Neither the first edition of Osler's textbook or the present year's edition of Osler's Modern Medicine mention the familial occurrence of gastric ulcer. It was not until the birth of the new medical philosophy of the *constitution* in the early years of this century that students of gastric ulcer began to take note of its multiple incidence in certain families. The first important observation upon this subject was that of Huber in 1907, who reported eleven cases of his own observation and nineteen seen by Bernhard. These observers were fully convinced of the fact of a hereditary predisposition to gastric ulcer; Huber thought it was present in 15 per cent of all cases, while Bernhard concluded that a hereditary predisposition was present in a third of his cases. In 1910 Czernecki reported a family in which a mother and two children all had gastric disease, all three of them with bleeding gastric ulcers, while two other children had hyperchlorhydria and gastric neuroses; all members of this family were of asthenic habitus and neuropathic. Westphal in 1914 collected fourteen cases, one-fourth of all his ulcer cases, in which there was multiple familial incidence of ulcer and gastric neuroses, with a high percentage of cases of carcinoma of the stomach. Plitek and Kodon also reported

observations on "ulcer families," noting the association of asthenic and neuropathic constitutions. R. Schmidt in 1916 observed in his clinic that the children of ulcer patients showed a multiple incidence of gastric ulcer. In the decade 1910-1920 the rapid development of constitution-pathology led to many observations on familial organ-predisposition, and a number of these were concerned with stomach conditions, gastric ulcer, hyperacidity, gastric neuroses, etc. (J. Bauer, Jung and others.)

In 1918 Ernst Spiegel made a special study of the question as to whether gastric disease was of more frequent occurrence in the families of ulcer patients than in the families of normal individuals. What is inherited is, of course, not gastric ulcer itself, but a pathological predispositon, and this may show itself in the form of ulcer, cancer, neurosis, or some other type of lowered gastric value. Spiegel studied the family history of 121 ulcer patients and 200 normal stomach individuals. He found that 74 (61.1 per cent) of the families of ulcer patients showed other cases of gastro-intestinal disease, while in the families of normal stomach individuals only 31 (15.5 per cent) showed other cases of gastric disease. In other words gastro-intestinal disease was nearly four times as frequent in the families of the ulcer patients as in the families of the non-ulcer cases. This study was carried out with the greatest care as regards intelligence of the patient, physiological consideration, age, state of nutrition, personal habits, etc. Of the families of ulcer patients 32 (26.4 per cent) showed ulcer symptoms, 18 (14.8 per cent) had carcinoma of the stomach, 4 (3.3 per cent) carcinoma of other portions of the gastro-intestinal tract, while 20 (16.5 per cent) had illy defined gastric disturbances. Comparing this with the families of non-ulcer cases ulcer in 11 (5.5 per cent), gastric cancer in 5 (2.5 per cent), cancer of other portions of gastro-intestinal tract in 2 (1 per cent), vague gastric symptoms in 13 (6.5 per cent) we find that ulcer symptoms are 5 times as frequent in the families of ulcer cases as in those of non-ulcer patients. Especially significant is the multiple occurrence of gastric carcinoma in the families of ulcer patients. In 121 ulcer patients' families there were 18 cases of gastric cancer—that is, every 7-8th ulcer patient showed a family history of gastric carcinoma. In the families of non-ulcer patients only every 40th gave a family history of carcinoma. Spiegel, therefore, concluded that the frequency of gastric disease, especially of gastric carcinoma, in the families of ulcer patients speaks for the important role played by constitutional organ inferiority in the pathogenesis of peptic ulcer. He does not conclude that all gastric and duodenal ulcers arise on the basis of a definite constitutional type, but that a certain proportion of such ulcers are definitely associated with the asthenic and lymphatic constitution. Siemens thinks that the rôle of the idiotype in the origin of peptic ulcer is not wholly clear. On the other hand Strauss believes that one-third of his cases show a definite familial occurrence. Grote makes a still stronger statement: he found evidence of a familial incidence

of ulcer in two-thirds of his cases. Bauer and Aschner believe that the constitutional susceptibility to peptic ulcer is recessive in character. The general constitutional peculiarities of individuals with gastric ulcer have been described by numerous writers. As early as 1913, Martius attempted to explain gastric ulcer on the ground of a spasmogenous etiology, associated with a definite constitutional factor "a spasmophilic disharmony of the vegetative nervous system," Czernicki also noted the incidence of ulcer in association with an asthenic-neuropsychopathic constitution. Strauss also noted constitutional peculiarities in the families of patients with peptic ulcer, especially the occurrence of a eunochoid or adiposogenitalis type. Constitutional anomalies endocrinal in nature are apparently more frequent in families showing a hereditary "weak stomach". They may exist without other characters of an asthenic constitution in the form of gastric neuroses or a neurodysergy. Bauer notes the association with peptic ulcer of constitional arterial disease, hyperacidity, lowered vitality of stomach wall, vasomotor excitability, motor disturbances secretory anomalies and various anomalies of the muscosa. In this country but little contribution has been made to the constitutional aspects of peptic ulcer. With all of the enormous clinical material of peptic ulcer seen by the Mayos, Smithies and others, their writings upon this subject are singularly devoid of any observations bearing upon familial occurrence or association with constitutional peculiarities. The same thing is true of the surgical histories of ulcer cases in the average American hospital. Taken usually by internes or inexperienced young assistants who lack any broad conception of constitution or constitutional peculiarities these important facts do not appear in these histories, and they are worthless as far as throwing any light upon the hereditary peculiarities of a given patient's family. Moreover, it is a mistake to try to obtain such facts from the patient himself. The writer has had the experience of receiving the clinical histories of ulcer and cancer cases, in which it was stated that the "family history is negative"; and then on inquiry from members of the family has found that the said family presented multiple cases of ulcer or cancer. In every one of the cases of peptic ulcer with which he has come into direct contact, he has found abundant evidence of the familial occurrence of gastric or duodenal ulcer, gastric cancer, or gastric disturbances associated with other anomalies of constitution. The familial "weak stomach" belief so firmly entrenched in the layman's mind has a definite foundation of fact underlying it. In this country, the academic discussion of the etiologic relationship of peptic ulcer to gastric cancer has received undue prominence and obscured the much more important constitutional aspects of this disease.

UNITED STATES PUBLIC HEALTH SERVICE

Seasonal Prevalence of Tularaemia.

Seasonal incidence of cases of tularaemia, according to the United States Public Health Service, is due to the seasonal variation of three sources

of infection, tick bite, fly bite and the dressing of wild rabbits, but owing to the overlapping of these influences, cases have occurred in the United States in every month of the year. The great reservoir of infection and the greatest source of human infection from tularaemia is the wild rabbits, jack, cottontail and snowshoe varieties, but owing to the agencies of blood sucking insects common to rabbits and man, we find cases resulting from tick bite and fly bite.

Of the rabbits offered for sale in the Washington, D. C., market in the winters of 1923, 1924, and 1925, Dr. Edward Francis of the Public Health Service examined the livers of 1,000 and found 9, or slightly less than 1 per cent, infected with tularaemia. The liver and spleen of an infected rabbit are studded over the surface with small spots varying in size from that of a pinpoint to one-sixteenth inch in diameter. Of 22 cases of tularaemia in Washington, 17 of the patients had dressed wild rabbits bought or sold in the market, 4 had dressed rabbits shot nearby, and one had dressed a rabbit which he had killed with a club.

Four hundred and twenty cases of tularaemia have been reported, of which 17 have died. This places the mortality at about 4 per cent. These figures embrace only the cases which have been reported to the Public Health Service, but considering the newness of the disease, they probably represent only a portion of the actual number of cases and deaths.

Cases have now been reported from Japan, from the District of Columbia and from 37 States. The nine northeastern States being the only significant portion of the United States in which cases have not been recognized.

As a rule when the infection has come from a rabbit some injury has been inflicted on the hand while dressing the rabbit, although a manifest injury is not necessary for infection to occur. Usually an ulcer develops at the site of infection accompanied by enlargement of the lymph glands which drain the ulcer. Fever is always present and continues for two or three weeks. The site of infection from tularaemia may be located on any part of the body other than the skin of the hands, if due to tick bite or fly bite. The diagnosis of tularaemia is confirmed by a blood test. One attack confers immunity in man. Rest in bed is the most important treatment. The enlarged lymph glands should be opened only after pus has definitely formed.

The infection has never been found in nature in domesticated rabbits raised in rabbitries.

No preventive vaccine or curative serum has yet been perfected, nor has any special drug been found effective against tularaemia.

Rabbit meat thoroughly cooked is harmless for food, and it has been found that a temperature of 56° Centigrade, of 133° Fahrenheit kills the germ of tularaemia. The ordinary disinfectants are effective. Rubber gloves should be worn by those who dress wild rabbits. Immune persons should be employed to dress them where possible. Infected rabbits, kept frozen for thirty days, have been found to be free from infection. Market inspection of

rabbits is impracticable, because only about 10 per cent of the rabbits found in the market still have the liver in place.

Beware of the wild rabbit which the dog or cat has caught, or which a boy has killed with a club,—it is probably a sick rabbit. The hunter should not shoot his rabbits at the point of his gun. Let him be a sportsman and shoot them on the run at 5 yards, say, and the chances will be lessened that the rabbits he bags will be sick with tularaemia.

Abstracts

Observations on the Cause of Gall-bladder Contraction and Evacuation. By A. C. Ivy and Eric Goldberg (Proc. of the Soc. for Exper. Biol. and Med., January, 1928, p. 251).

In a previous communication these writers had shown that purified extracts of the duodenal and jejunal mucosa when injected intravenously cause the gall-bladder to contract and to exert pressure on its contents and at the same time excite the pancreas to secrete. Since that report Kloster, Lueth and Ivy have made preparations the use of which indicates that "secretin" does not cause the gall-bladder to contract, but that it is some substance closely associated with secretin, because it is possible to prepare a solution of secretin which is free of the gall-bladder excitant. In more than ten experiments the writers observed the gall-bladder to contract when 20 or 30 cc. of N/10 HCl were introduced into the duodenum, the cystic duct having been clamped and the gall-bladder cannulated under barbital anesthesia. The latent period of contraction was in most cases less than 2 minutes, whereas the latent period for the pancreatic response varied from 5 to 10 minutes. Cross-circulation experiments were performed as follows: 2 compatible dogs were given barbital and placed on the table side by side; the pancreatic duct of each animal was cannulated; the cystic duct of each was clamped and the gall-bladder cannulated and attached to a manometer and recording tambour; the most lateral carotid of each animal was prepared for a blood-pressure record, and the medial carotids were connected with cannulae for cross-circulation. In 3 out of 4 experiments the introduction of 40 cc. of N/10 HCl into the duodenum of one dog caused the gall-bladder of the second dog to contract after a period of from 8-10 minutes. These experiments would indicate that the introduction of the acid into the duodenum of the "first" animal caused something to enter its blood, which passed via the cross-circulation to the "second" animal, causing the latter's gall-bladder to contract. The pancreas of the second dog was only slightly stimulated in one experiment. These experiments tend to show that a hormone mechanism must be considered at least as one of the mechanisms concerned in the normal contraction and evacuation of the gall-bladder. The authors propose the term "cholecystokinin" as a designation for the principle which causes the gall-bladder to contract.

Effect of Kidney Diet on Blood Regeneration in Pernicious Anemia. By Wm. S. McCann (Proc. Soc. for Exper. Biol. and Med., January, 1928, p. 255).

The experiments of Whipple and Robscheit-Robbins have shown the effects of various articles of diet on the regeneration of blood in dogs rendered chronically anemic by repeated bleeding. The most important application of this fundamental work to the therapy of anemia was made by Minot and Murphy in the administration of liver in pernicious anemia, with remarkable results that have been abundantly confirmed. It is desirable to ascertain if other foods, particular kidney and apricots, which caused active regeneration in anemic dogs, have a similar therapeutic action upon man. This paper reports the results obtained by the feeding of 250 gm. of kidney daily to two cases of pernicious anemia. The diets contained no red muscle, and no other food beside kidney known to be of high value in blood regeneration, except small amounts of apricots, prunes and other fruits, given as desserts. Both patients had remissions induced by the kidney diet. The

relative values of kidney and liver feeding can, however, be determined only through the comparison of a long series of cases.

Origin of the Blood Monocyte. By WILLIAM BLOOM (Proc. Exper. Biol. and Med., January, 1928, p. 244).

The monocytes of the blood were studied in normal rabbits as well as those in which a monocytosis was produced by intravenous injections of india ink, lithium carmine and saccharated iron, and by infecting the rabbith with *B. monocytogenes* recently isolated by Murray, Webb and Swan. Some of the infected rabbits were also injected with lithium carmine, while others were splenectomized. Two of the latter were slowly injected with one quarter of a cc. of Higgins' india ink in a branch of the portal vein, so that the carbon would accumulate in the endothelial cells of the liver sinusoids. Great numbers of monocytes are produced in the rabbit by the methods used. These monocytes are typical of the monocyte of the rabbit as described by Simpson and Sabin, Doan and Cunningham, etc. In all of the vessels of the animal, but particularly in those of the liver and spleen, the monocytes are always accompanied by large numbers of lymphocytes and monocytoid lymphocytes. These latter are so numerous and form such a complete series of transition forms between the lymphocytes and monocytes that the conclusion becomes unavoidable that the monocytes develop by individual transformation of the lymphocytes. The author paid particular attention to the relations of the vascular endothelium, reticulum endothelium and fibroblasts to the monocytes, and found no evidence of any of those fixed cells turning into monocytes. The development of the fixed cells into free macrophages could be followed in his sections. Although the monocytes do not contain carmin, they can develop into carmin-staining macrophages. The evidence of the author's experiments shows that the monocytes develop from lymphocytes within the blood vessels all over the body and that the sinuses of the spleen are richest in the cells showing this transformation. The numerous mitoses in the lymphocytes in the lymphoid tissue are sufficient to account for the numbers of new cells necessary to produce the monocytosis; there is no such increase in numbers in any of the fixed cells. When the spleen is removed and india ink injected into the portal vein, the lymphocytes in the lymphnodes and bone-marrow develop neutral red rosettes and show evidences of turning into monocytes before they leave the organs in which they are produced and before leaving the blood stream.

General Tuberculin-like Reactions in Rheumatic Fever Patients Following Intravenous Injection of Streptococcus Vaccines or Nucleoproteins. By HOMER F. SWIFT, CHARLES H. HITCHCOCK and CLIFFORD L. DERICK (Proc. Soc. Exper. Biol. and Med. January 1928, p. 312).

Some years ago Swift suggested that rheumatic fever had many points of similarity with tuberculosis. Since then it has been shown by him and his associates that rabbits may be rendered hypersensitive to streptococci by the production of focal lesions with various types of hemolytic streptococci isolated from rheumatic fever and other diseases. As these streptococci have been shown to belong to various immunological groups the hypothesis was formulated that if they had any etiologic relationship with the disease it was because of a peculiar type of tissue activity acquired by the rheumatic patient. They have, therefore, tested the reactivity of a number of patients in the late stage of rheumatic fever to intravenous injections of streptococci or products derived from them, heat-killed suspensions, vaccines prepared from both green and hemolytic streptococci, and nucleoproteins made from hemolytic streptococci. In all instances the initial dosage was very small and subsequently increased by slow degrees in order to avoid too severe reactions. The type of febrile reaction was uniform, and consisted, as a rule, of slowly rising temperature which usually did not begin until 6-8 hours after the injections, and often did not reach its maximum until from 16-30 hours. In a few instances the fever persisted for 2-4 days, but as a rule it has disappeared by

the end of 36 hours. There was an accompanying increase in pulse rate, often headache, dizziness and general malaise. Chills and chilly sensations were rare. In some cases there was moderate reactivation of previously quiescent arthritis, and symptoms pointing to activation of cardiac foci. These reactions are strongly suggestive of the late reactions observed in tuberculous patients after injections of tuberculosis. They are distinctly different from the non-specific shock reactions observed in control cases, and that others have observed in rheumatic patients following intravenous injection of typhoid vaccine. In the latter instance the reaction is usually ushered in by a chill within 1-4 hours after the injection; this is followed within 1-3 hours by the peak of the fever, which soon subsides. The reaction following the use of typhoid vaccine was usually completed in 10 hours or less. Small also has observed similar late general reactions 24-48 hours after subcutaneous injection of rheumatic fever patients with vaccines of *Strept. cardioarthritides* described by him. At times these reactions were very severe. In their focal features they were strongly suggestive of tuberculin-like reactions. Swift and his associates feel justified in assuming that the patients showing these peculiar general and focal reactions, following injections of these streptococci and their products, have a tuberculin-like allergy (hyperergy) towards streptococci, and that probably this altered tissue reaction accounts for many of the peculiar characters of this disease.

A Further Study of Gye's Hypothesis on the Etiology of Malignant Tumors. By John A. Kolmer and Malcolm J. Harkins. (The Jour. of Cancer Research, October, 1927, p. 217).

Nearly two years have elapsed since Gye made his announcement that the cause of all malignant new growths of man and the lower animals is a filterable but cultivatable ultramicroscopic microbe, which, however, is unable to produce tumors unless the resistance of the host is first specifically reduced by a second cellular product or "chemical stimulant" called the "specific factor," so designated because the latter and not the microbe was held by him to determine the kind and species specificity of of tumors. No confirmation of Gye's work has up to the present time been obtained by any worker; indeed all experimental work carried out on the lines indicated by his investigations have led to results negativing both his technique and his conclusions. The present paper repeats Gye's work and led to the following conclusions:

1. The infectivity of the Rous fowl sarcoma is usually completely destroyed by treating sand-paper and Berkefeld filtrates of 5 per cent tumor suspension with 5 per cent chloroform or 1:5000 acriflavine for 6 hours at 30°C., likewise by heating at 55-56° for 18 minutes.

2. Inoculation of Plymouth Rock chickens with subcultures of fowl sarcoma and 5 per cent chloroform treated filtrates have produced no tumors.

3. Inoculation with subcultures and 1:5000 acriflavin treated filtrates produced no tumors.

4. Inoculation with chloroform and heat treated filtrates produced no tumors.

5. Inoculation with acriflavin and heat treated filtrates have with one exception produced no tumors.

6. Substitution experiments employing mouse sarcoma 37/S yielded negative findings.

7. The results are interpreted as failing to confirm Gye's hypothesis on the etiology of malignant new growths.

No results were obtained in this investigation that would cause these workers to change their previous conclusion that Gye's "specific factor" is in reality nothing more than a suspension of attenuated living virus which may or may not produce a tumor depending upon the fowl's susceptibility or resistance.

Reviews

Practical Bacteriology, Blood Work and Animal Parasitology. Including Keys, Zoological Tables and Explanatory Clinical Notes. A Compendium for Internists. Eighth Edition, Revised and Enlarged. By E. R. Stitt, A.B., Ph.G., M.D., Sc. D., LL.D., Rear Admiral, Medical Corps, and Surgeon General, U. S. Navy; President National Board of Medical Examiners; Member Federal Board of Hospitalization; Formerly Commanding Officer and Head of Department of Tropical Medicine, U. S. Naval School; Professor of Tropical Medicine, Georgetown University; Professor Tropical Medicine, George Washington University; Lecturer in Tropical Medicine, Jefferson Medical College; Associate Professor of Medical Zoology, University of the Phillipines. 837 pages, 1 plate and 211 other illustrations containing 683 figures. P. Blakiston's Son & Co., Philadelphia, 1927. Price in cloth, $6.00.

In the production of this new edition the author attempted to reduce its size, but because of the important additions to our knowledge along the line of clinical pathology in the last four years, it proved necessary to increase by about the same number of pages it had been planned to reduce it. This work began as a laboratory manual in clinical pathology prepared to serve as a textbook for the student officers at the Naval Medical School, and in each revision the author has been guided by his experience in teaching, and by the criticisms of students and suggestions from the instructors at the Naval Medical School. Numerous changes have been made in the material used for this new edition. Keys have been added giving the nomenclature approved by the Society of American Bacteriologists, the old names in parentheses following the new ones. In the subject matter the new name is given following the long accepted designation. Chapters on the methods of medical and dental cooperation practiced in the Navy and Navy Schools have been incorporated. Since the Kahn test has been made standard in the Navy since December, 1925, a comprehensive description of the method and variations, prepared by Dr. Kahn, has been incorporated. Particular attention is invited to the many additions and changes under the streptococcus group—particularly those bearing on scarlet fever, measles, erysipelas and poliomyelitis. Some of the most important changes in this edition have been in Part II, Study of the Blood. The older methods of cell counting and other technical procedures have been replaced by more recent ones. The sedimentation test is extensively discussed in this chapter. In Chapter XIV a new section on the hemorrhagic diseases has been added, with new material on sicklecell anemia and glandular fever. In Part III the changes in zoological nomenclature have been almost as great as with the bacteria. An entirely new section on liver-function tests, prepared by Lt. W. W. Hall, has been added. The section on nutrition in health and disease has been revised by Commander Phelps; while the section on disinfectants and insecticides has been brought up to date by Setterstrom. Many other changes and additions are scattered through the book. The presentation of the abundant material is necessarily much condensed, but the main facts are presented in a clear and concise form. It is a very practical manual of clinical pathology, particularly well adapted for its main purpose —its use in the Naval Medical School and in Naval laboratory work. It is well-printed, in a convenient form; its illustrations are many and adequate. It covers such a wide extent of ground that it may

be of great use to the regular medical student and internist as well.

Recent Advances in Tropical Medicine. By SIR LEONARD ROGERS, G.T.E., M.D., B.S. (Lond.), F.R.G.P., F.R.C.S., F.R.S., Indian Medical Service, Ret. Physician and Lecturer London School of Tropical Medicine; Lecturer on Tropical Medicine, London School of Medicine for Women; Late Professor of Pathology, Medical College, Calcutta. 398 pages, 12 illustrations, P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, $3.00.

Tropical Medicine is not now making the giant strides that it did twenty-five years ago, but there has been nevertheless a definite progress made in all parts of the world. The heavy task of summarizing the more important recent advances in tropical medicine have been made possible largely through the abstracts published in the Tropical Diseases Bulletin and in the Medical Annual. The author has given especial prominence in this little book to treatment and to other points of most practical importance to the isolated man in the tropics, rather than to the minute pathology and laboratory technique, which he so rarely has the facilities or the time to make use of. He hopes that this compilation may help to lighten the labors of the scattered bearers of the white man's burden throughout the Empire. The twenty-three chapters treat in order, of Kala-azar, Dermal Leishmaniasis, Malaria, Blackwater Fever, Trypanosomiasis, Relapsing Fever, Yellow Fever, Dengue and Phlebotomous Fevers and Tick Typhus, Undulant Fever, Plague, Cholera, Bacillary Dysentery, Flagellate Diarrhea, Abiasis, Amebic Hepatitis and Liver Abscess, Sprue, Ankylostomiasis or Hookworm Disease, Schistosomiasis, Filariasis, Leprosy, Yaws, Beriberi and Pellagra. The material in these chapters is recent, well condensed and concisely presented. The convenient size of the volume makes it a very handy manual on these most important of the tropical diseases, and should be of use to the general medical student in the subtropical and temperate zones, as well as to the student in the Naval schools and hospitals. The treatment of the material is eminently practical and general aims of the author are satisfactorily accomplished.

Recent Advances in Haematology. By A. PINEY, M.D., Ch.B. (Birm.); M.R.C.P. (Lond.), Research Pathologist, Cancer Hospital, London; late Director of the Charing Cross Hospital Institute of Pathology, London; sometime Lecturer in Pathological Histology in the University of Birmingham. 276 pages, 4 colored plates and 18 text figures. P. Blakiston's Son and Company, Philadelphia, 1927. Price in cloth, $3.50.

The modest preface to this little book craves the indulgence of the reader for its deficiencies, since the writer believes that the production of an adequate book dealing with the recent advances in hematology would require an almost encyclopedic knowledge of the vast literature of the subject. He has therefore attempted only to give indications of what he regards as being the present position of a number of hematological subjects, but has not tried to include every aspect of the science, nor has he been able to make reference to all the investigators who have contributed to our knowledge of the subject. There are fourteen chapters, dealing respectively with an introduction, the reticulo-endothelial system, development of blood cells, leukemia, pernicious anemia, leukemoid blood pictures, leukemoid reactions, reticulo-endotheliosis, polycythemia, hemorrhagic diatheses, symptomatic changes, Gaucher's disease, Banti's disease, acholuric jaundice and anemia pseudo-leukemica infantum. There follow then a summary, an Appendix I, dealing with hematological technique, and a second Appendix treating of textbooks and monographs on the subject, and finally the index. The book is in truth only a manual, and possesses all of the faults of incompleteness that manuals usually show. There is a great unevenness in the treatment of the various subjects; some of these, such as polycythemia, the leukemic and aleukemic lymphoblastomas, Banti's disease, etc., being very inadequately treated. The author seems to be familiar only with recent hema-

tological literature, and, therefore, many of the important facts of hematology already recorded have escaped his notice, and he introduces other ideas as if he were the original discoverer of them, although most of them have been in the literature for thirty years or more. He has shown good judgment in his support of the modern conceptions of the familial susceptibility to pernicious anemia, to the neoplastic character of the leukemic and aleukemic lymphoblastomas and myeloblastomas, and of Hodgkin's disease; but his general treatment of the subject is somewhat amateurish, and, although readable and interesting, not very helpful from any practical standpoint. The eighteen illustrations of the book are extremely poor and might better have been omitted, for any illustrative value they possess.

Recent Advances in Medicine. Clinical Laboratory Therapeutic. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Assistant Physician to the Middlesex Hospital; Lecturer in Practical Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Travelling Fellow, University of Oxford; and E. C. Dodds, M.D., B.S., Ph.D., B.Sc. (Lond.), Professor of Biochemistry in the University of London; Chemical Pathologist to the Middlesex Hospital, Bland-Sutton Institute of Pathology; Chemical Pathologist to the City of London Maternity Hospital; Pathologist to the Royal National Orthopedic Hospital. Third Edition. 408 pages, 46 illustrations. P. Blakiston's Son and Company, Philadelphia, 1926. Price in cloth, $3.50.

Three editions of this work have been necessary in two years. In this, the third, alterations have been made in the arrangement of the book. An introductory chapter has been added dealing with clinical investigations, as an indication of the value of the methods subsequently described and their practical application. The clinical portions of the book have been expanded; a section has been added on the after-care and treatment of diabetic patients, and the graduated diets have been set out in the form of the daily meals so that their practical application is facilitated. The investigation of the condition of the gall bladder by means of cholecystograms and the use of lipiodol injections in diseases of the lungs have been described. These two sections are illustrated by X-ray plates. Further alterations and additions include the recent work on the van den Bergh test, the galactose test for liver function, and an amplification of the description of the phenoltetrachlorphthalein test for liver function. The chapter on Blood Analysis is now placed at the end of the book, and in order to make this section complete the colorimetric methods of urinary analysis have been included. The special blood examinations are now described in a separate chapter, and the article on blood transfusion has been amplified to include the recent work on blood grouping. This is of importance as showing the further precautions which have been found necessary before a transfusion is carried out to avoid the risk of death from incompatibility. This book, as it now stands, is a very valuable and convenient manual of clinical laboratory procedures, both diagnostic and therapeutic. Care has been taken to give a workable description of each procedure; all techniques described have been personally performed by one or the other author, and the accounts are taken from their note-books. While sometimes differing from the original descriptions the methods described have been used by the authors as a routine for some time and have yielded them satisfactory results. They have also attempted to evaluate the results obtained by the various tests. The guiding principle has been to describe such methods of diagpatients in a general hospital and which can nosis and treatment as are used for medical be justly termed "recent advances in medicine."

College News Notes

By direction of the President, Dr. Frank Smithies, a meeting of the Board of Regents is called for Saturday, March 3, 2:00 P. M., Roosevelt Hotel, New Orleans, La.

Heretofore the meetings of the Board have been delayed until the Clinical Session had begun, with the result that elections to Fellowship were delayed and hurried, members of the Board could not attend many of the general sessions and clinics, and insufficient time was available for the discussion and determination of College problems and policies.

Members of the Committee on Credentials are asked to meet Saturday morning, March 3, 9:00 o'clock, to examine all applications for Fellowship and prepare recommendations to the Board of Regents for disposal of the same. Any members of the Committee on Credentials who reach New Orleans Friday, March 2, are asked to arrange with the Executive Secretary to start at once on the examination of these applications, in order to facilitate the completion of this important and lengthy task.

Reservations for all members of the Board of Regents have been made at the Roosevelt Hotel.

OBITUARY

Dr. Charles Erastus Darrow (Fellow, February 23, 1920) died suddenly in Rochester, New York, on January 2, 1928, of Angina Pectoris.

Dr. Darrow was born in Rochester on December 3, 1855. He received his early and academic education at the Satterlee Private School, of Rochester and at the University of Rochester, from which he was graduated with the degree A.B., in 1877, being also elected to Phi Beta Kappa. Later he received the degree A.M. from the same university. He studied for one year at the Jefferson Medical College, in Philadelphia, and was graduated from the College of Physicians and Surgeons, the Medical Department of Columbia University, in 1881, with the degree M.D. He began the practice of medicine in Rochester immediately after his graduation. For many years he was one of the visiting physicians to the Rochester City Hospital, later the Rochester General Hospital, and on reaching the age of 65 years, in 1920, was made one of the consulting physicians of the hospital.

Dr. Darrow was preeminently a member of the fast disappearing group of family physicians, and retained the loyal support of a large clientele until the day of his death, which occurred during the course of his regular visits to his patients. The greater part of his work belonged to the department of Internal Medicine, although in his younger days he is credited with having devised several practical surgical instruments. He was much interested in the serum treatment of tuberculosis, elaborating a method of his own which he used in his practice for several years.

A search of the literature shows that in 1866 he contributed a paper to the American Journal of Obstetrics, entitled "A Practical Self-retaining Sim's Speculum." 19:595; and to the New York State Journal of Medicine, in the October issue of 1905, a paper entitled "Bronchopneumonia."

An editorial in the Rochester Democrat and Chronicle for January 6th said: "* * * There is a type of physician who sees his profession as a great opportunity for lightening the human load. Dr. Darrow was of that type. He had the sympathy, the natural love for his fellow beings, the innate kindliness that added potency to the medicaments he prescribed. These qualities, linked with a skill in his profession that commended wide attention, explain the

unaffected grief with which the large circle of his friends heard of his sudden passing."

Dr. Darrow, in addition to being a Fellow of the American College of Physicians, was a Fellow of the American Medical Association; a member of the Medical Society of the State of New York, and the Medical Society of the County of Monroe, a Fellow of the Rochester Academy of Medicine, and a member of the Rochester Medical Association and the Rochester Pathological Society.

In 1909, Dr. Darrow was elected vice-president of the Medical Society of the County of Monroe, and in 1910 its president. In 1911, at the conclusion of his term as president, he was elected a censor of the Society and served in that capacity until 1914.

(Contributed by Dr. John M. Swan, F. A. C. P., Rochester, New York.)

Dr. Irwin C. Sutton, Hollywood, Calif. (Associate, March 10, 1923).

Died January 25, 1928; aged 31, M.D., College of Physicians and Surgeons, Los Angeles, 1919; postgraduate study, Mayo Clinic and Johns Hopkins Hospital.

CONFERENCE ON RHEUMATIC DISEASES

A Conference on Rheumatic Diseases is to be held at Bath, England, on Thursday and Friday, May 10th and 11th, 1928. Sir George Newman, Chief Medical Officer of the British Ministry of Health, has kindly consented to act as President of the Conference. There will be three Sessions: (1) Social Aspects, presided over by Lord Dawson of Penn, Physician to H. M. King George, (2) Causation, presided over by Sir Humphry Rolleston, (Regius Professor of Physic, University of Cambridge), and (3) Treatment presided over by Sir E. Farquhar Buzzard, (Regius Professor of Medicine, University of Oxford). The local Hon. Medical Secretary is Dr. Vincent Coates, 10, Circus, Bath, England.

SPECIAL ANNOUNCEMENT

The 13th Annual Convention of the Catholic Hospital Association of the United States and Canada and the Second Annual Hospital Clinical Congress of North America will be held in the Cincinnati Music Hall, Cincinnati, Ohio, June 18th to 22nd, inclusive, 1928. The Fourth Annual Convention of the International Guild of Nurses will be held at the same time, in the same building, at night meetings.

This Convention and Congress will be one of the largest and most important hospital meetings of the year, and will comprise general scientific meetings, special clinics or demonstrations of hospital departments, and three hundred special commercial and educational exhibits. Outstanding authorities in medicine, surgery, pathology, nursing, dietetics and hospital administration, architecture and engineering will lecture and demonstrate in specially planned clinics representing the various departments of the modern hospital. A professional program of the highest interest and value is now being formulated, and all persons interested in medical and hospital service are cordially invited to attend. Further information may be obtained from John R. Hughes, M.D., Dean of the College of Hospital Administration, Marquette University, Milwaukee, Wisconsin, who is General Chairman of the Convention and Congress.

Meeting of

THE AMERICAN COLLEGE OF PHYSICIANS

NEW ORLEANS, MARCH 5-9, 1928

PROGRAM

Corrected and Brought Up to Present Date

MORNING SESSION, MONDAY, 10:00

Address of Welcome, Mayor Arthur O'Keefe.

Address of Welcome, President A. B. Dinwiddie, Tulane University.

Address of Welcome, Dr. J. Birney Guthrie, President, Orleans Parish Medical Society.

Address of Welcome, Dr. C. C. Bass, Dean, Tulane University School of Medicine.

1. Dr. Julius Bauer, Vienna, Austria, "Adaptation and Compensation as Origin of Disorders."

2. Dr. David P. Barr, "Multiple Myeloma."

3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer, "Cardiac Conditions Contraindicating the Use of Digitalis."

5. Dr. Frank R. Menne, "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Sly, "Cancer and Heredity."

2. Dr. Aristides Agramonte, Havana, "Review of Research in Yellow Fever."

MORNING SESSION, TUESDAY, 10:00

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, "The Treatment of Pernicious Anemia with a Liver Fraction."

Symposium on Tuberculosis.

5. Dr. Charles L. Minor, "Modern Trends in the Treatment of Tuberculosis."

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

EVENING SESSION, TUESDAY—7:45

1. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

2. Dr. James S. McLester, "The Influence of Latent Syphilis, So-called, upon the Course of Other Diseases."

MORNING SESSION, WEDNESDAY—10:00

1. Dr. Walter M. Simpson, "Tularemia: A Clinical and Pathological Study of Fifteen Non-Fatal Cases and One Rapidly Fatal Case with Autopsy."

2. Dr. L. F. Bishop, "The Practice of Cardiology."

3. Dr. Morris H. Kahn, "Heart Strain and Its Consequences."

4. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

Symposium on Epilepsy.

5. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

6. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

7. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

EVENING SESSION, WEDNESDAY—7:45

Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."

MORNING SESSION, THURSDAY—10:00

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."

2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."

3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the View Point of an Internist."

Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."

5. Dr. Frederick M. Allen, "Present Results and Outlook of Diabetic Treatment."

6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."

7. Dr. W. H. Olmsted, "The Dietetic Management of the Diabetic in the Doctor's Office."

Morning Session, Friday—10:00

1. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."

2. Dr. T. Z. Cason, "The Progress of Medical Research in the South."

Symposium on Tropical Medicine.

3. Colonel Roger Brooke, "The Influence of the Tropics on Rickets."

4. Dr. Aldo Castellani, "Metadysentery, with Remarks on the Classification of Intestinal Bacteria."

5. Dr. Wm. M. James, "The Early Lesions of Intestinal Amebiasis."

6. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.

7. Dr. Aristides Agramonte, "Considerations upon the Etiologic Agent of Yellow Fever."

Evening Session, Friday—7:45

1. Dr. Julius Bauer, Vienna. Convocation Address—"Multiplicity of Factors in the Etiology of Disease."

January 17, 1928.

Dr. E. R. Loveland, Executive Secretary,
The American College of Physicians,
Philadelphia, Pennsylvania.

Dear Dr. Loveland:

You will recall that the Governor, the Mayor-Municipality, the Medical College of Virginia and the Richmond Academy of Medicine presented invitations to the American College of Physicians, at their meeting in Detroit, asking that the 1928 convention be held in the unique, historic city of Richmond, which is also one of the most prominent medical centers in the South.

We are still desirous of having our City and State honored with one of your meetings and want to impress this upon those having the selection of the city for the 1929 meeting.

Many of the scientific branches of medicine and surgery, with organized units, have honored Richmond and all of them have expressed themselves most generously with the cordiality, hospitality and success of the meetings.

We have a Medical College, the oldest in the South, which is preparing to enlarge extensively; many standard hospitals and a city unique with a background of history and many shrines of interest particularly to those engaged in science in the spirit of the American institutions.

Six trunk-line railways lead to Richmond and several of the national highways traverse some of the most beautiful sections of our country and in line with many other points of interest in our City and State.

Our hotel facilities are unsurpassed, one in particular is said to be the best arranged in the United States for holding such meetings, with an auditorium seating 1000 people on the mezzanine floor, numerous committee rooms and a lobby extending from street to street the width of the hotel for intercourse during recess or after the meetings.

We have three delightful club golf course links the courtesy of which is cordially extended representative citizens in our midst.

I feel sure, should Richmond be honored, that you will find every agency with open hands and hearts ready to facilitate and cooperate in any way possible to make the occasion one of unusual success.

Very truly yours,
Richmond Chamber of Commerce
W. T. Dabney, Business Manager.